TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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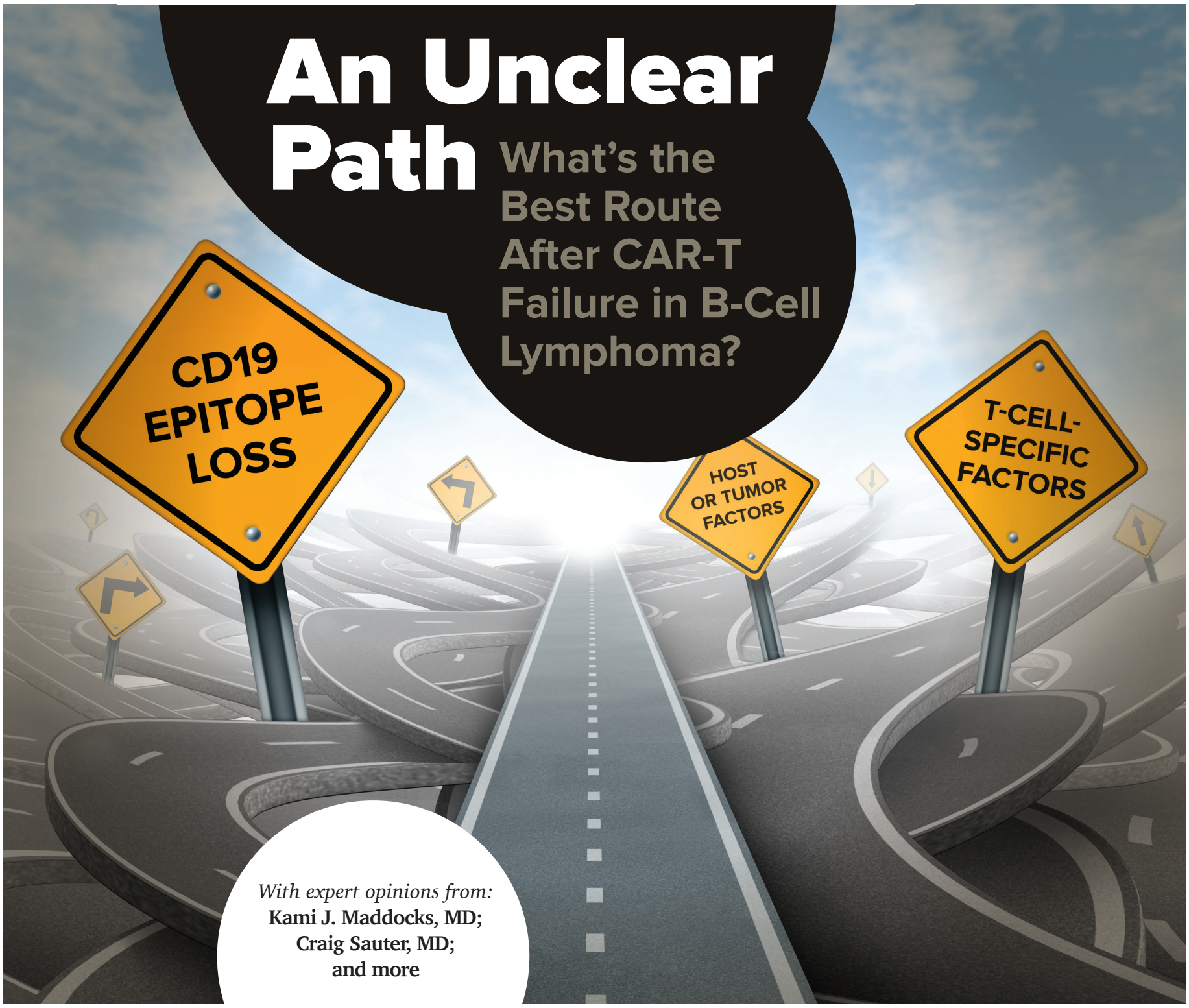
An Unclear Path

What's the Best Route After CAR-T Failure in B-Cell Lymphoma?



With expert opinions from:
Kami J. Maddocks, MD; Craig Sauter, MD; and more

MAIL TO:

ASSOCIATE EDITOR LAURIE H. SEHN, MD, MPH:

How to Choose the Right Treatment When There Are So Many Options in DLBCL

An official publication of
soho
society of hematologic oncology

ZYNLONTA® is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this

*__Study design:__ **Phase 2 open-label, single-arm trial (N=145)** to evaluate the efficacy and safety of ZYNLONTA as a monotherapy in r/r DLBCL after 2 or more systemic therapies. Patients received 0.15 mg/kg Q3W for 2 cycles with dexamethasone premedication (unless contraindicated), then 0.075 mg/kg Q3W for subsequent cycles. Primary endpoint was ORR, evaluated by independent review committee using Lugano 2014 criteria. ZYNLONTA was administered until progressive disease or unacceptable toxicity.[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Effusion and Edema Serious effusion and edema occurred. Grade 3 edema: 3% (primarily peripheral edema or ascites); Grade 3 pleural effusion: 3%; Grade 3/4 pericardial effusion: 1%.

Monitor patients for new/worsening edema or effusions. Withhold ZYNLONTA® for Grade >2 until toxicity resolves. Consider diagnostic imaging in patients with symptoms of pleural or pericardial effusion, such as new/worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management.

Myelosuppression Serious or severe myelosuppression—including neutropenia, thrombocytopenia, and anemia—occurred. Grade 3/4 neutropenia: 32%; thrombocytopenia: 20%; anemia: 12%. Grade 4 neutropenia: 21%; thrombocytopenia: 7%. Febrile neutropenia occurred: 3%.

Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA®. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Infections Fatal and serious infections, including opportunistic infections, occurred. Grade ≥3: 10%; fatal infections: 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia.

Monitor for any new/worsening signs or symptoms consistent with infection. For Grade 3/4 infection, withhold ZYNLONTA® until infection has resolved.

Cutaneous Reactions Serious cutaneous reactions occurred. Grade 3: 4%, including photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.

Monitor patients for new/worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA® for Grade 3 until resolution. Advise patients to: minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows; protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, consider dermatologic consultation.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.
You may also report side effects to ADC Therapeutics at 1-855-690-0340.

AR = adverse reaction; CI = confidence interval; CR = complete response; DOR = duration of response; ORR = overall response rate; NE = not estimable; PR = partial response; r/r = relapsed or refractory

ADC THERAPEUTICS

or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Challenge expectations in 3L DLBCL

Take the next step...

...on the path to response with the first and only *single-agent,* CD19-directed ADC[1,2]

48.3% ORR[a*†‡]
(95% CI: 39.9, 56.7)[1]
24.1% CR; 24.1% PR[‡]
(95% CI for each: 17.4, 31.9)[1]

1.3 Months
median time to response
(range: 1.1–8.1)[1]

Single-Agent IV[1,b]
30-minute infusion
Once every 3 weeks

[a] **Median duration of response:** 10.3 months (95% CI: 6.9, NE). Of 70 patients with objective response, 25 (36%) were censored prior to 3 months; 26% of responders had a DOR of ≥6 months.[1]

[b] **Premedication:** dexamethasone 4 mg (oral or IV) twice daily for 3 days, beginning the day before infusion. If dexamethasone administration does not begin the day before ZYNLONTA, it should begin at least 2 hours prior to ZYNLONTA infusion (unless contraindicated).[1]

[†] **Median follow-up time:** 7.3 months (range: 0.3–20.2).[1]

[‡] **ORR:** n=70. **CR:** n=35. **PR:** n=35.[1]

Embryo-Fetal Toxicity ZYNLONTA® can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells.

Advise pregnant women of potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA® and for 10 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA® and for 7 months after the last dose.

ADVERSE REACTIONS In a pooled safety population (215 patients, Phase 1 and LOTIS-2), the most common (>20%) ARs, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase (GGT), neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

In LOTIS-2, serious ARs occurred in 28% of patients. The most common (>2%) were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis.

Fatal ARs: 1%, due to infection.

Please see Brief Summary of the full Prescribing Information on adjacent pages.

www.zynlontahcp.com

Permanent treatment discontinuation due to an AR of ZYNLONTA®: 19%. Of these, ≥2% were increased GGT, edema, and effusion.

Dose reductions due to an AR of ZYNLONTA®: 8%. Of these, ≥4% was increased GGT.

Dosage interruptions due to an AR of ZYNLONTA®: 49%. Of these, ≥5% were increased GGT, neutropenia, thrombocytopenia, and edema.

DOSAGE MODIFICATIONS AND DELAYS

Recommended Dosage Modifications for Adverse Reactions For Grade ≥3 nonhematologic toxicity, hold ZYNLONTA® until toxicity ≤Grade 1. For neutropenia: if ANC <1 x 10^9/L, hold ZYNLONTA® until ANC ≥1 x 10^9/L. For thrombocytopenia: if platelet count <50,000/mcL, hold ZYNLONTA® until ≥50,000/mcL. For Grade ≥2 edema or effusion, hold ZYNLONTA® until ≤Grade 1.

Recommendations for Dosage Delays If dosing is delayed >3 weeks due to toxicity related to ZYNLONTA®, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation. Note: If toxicity requires dose reduction following second dose of 0.15 mg/kg (C2D1), patient should receive 0.075 mg/kg for Cycle 3.

Zynlonta®
loncastuximab tesirine-lpyl
for injection, for intravenous use • 10mg

ZYNLONTA® (loncastuximab tesirine-lpyl) for injection, for intravenous use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

INDICATIONS AND USAGE

ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Effusion and Edema. Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1%. Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

Myelosuppression. Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%. Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Infections. Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia. Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

Cutaneous Reactions. Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema. Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

Embryo-Fetal Toxicity. Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 10 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA, and for 7 months after the last dose.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

Effusion and Edema

Myelosuppression

Infections

Cutaneous Reactions

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 215 patients with DLBCL in studies ADCT-402-201 (LOTIS-2) and ADCT-402-101, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles.

In this pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

LOTIS-2. The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies. The trial required hepatic transaminases, including gamma-glutamyltransferase (GGT), ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and creatinine clearance ≥60 mL/min. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease or unacceptable toxicity. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles. The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.

Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.

Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

Table 1 summarizes the adverse reactions in LOTIS-2.

Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2

Adverse Reaction	ZYNLONTA (N=145)	
	All Grades (%)	Grades 3 or 4 (%)
General Disorders and Administration Site Conditions		
Fatigue[b]	38	1[a]
Edema[c]	28	3[a]
Skin and Subcutaneous Tissue Disorders		
Rash[d]	30	2[a]
Pruritus	12	0
Photosensitivity reaction	10	2[a]
Gastrointestinal Disorders		
Nausea	23	0
Diarrhea	17	2[a]
Abdominal pain[e]	14	3
Vomiting	13	0
Constipation	12	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[f]	23	1[a]
Metabolism and Nutrition Disorders		
Decreased appetite	15	0
Respiratory Disorders		
Dyspnea[g]	13	1[a]
Pleural effusion	10	2[a]
Infection		
Upper respiratory tract infection[h]	10	<1[a]

[a] No Grade 4 adverse reactions occurred

[b] Fatigue includes fatigue, asthenia, and lethargy

[c] Edema includes edema, face edema, generalized edema, peripheral edema, ascites, fluid overload, peripheral swelling, swelling, and swelling face

[d] Rash includes rash, rash erythematous, rash maculopapular, rash pruritic, rash pustular, erythema, generalized erythema, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative generalized, and palmar-plantar erythrodysesthesia syndrome

[e] Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper

[f] Musculoskeletal pain includes musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, back pain, limb discomfort, myalgia, neck pain, non-cardiac chest pain, and pain in extremity

[g] Dyspnea includes dyspnea, and dyspnea exertional

[h] Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract congestion, nasopharyngitis, rhinitis, rhinovirus infection, and sinusitis

Clinically relevant adverse reactions in <10% of patients (all grades) who received ZYNLONTA included:

- Blood and lymphatic system disorders: Febrile neutropenia (3%)
- Cardiac disorders: Pericardial effusion (3%)
- Infections: Pneumonia[a] (5%), sepsis[b] (2%)
- Skin and subcutaneous disorders: Hyperpigmentation (4%)
- General disorders: Infusion site extravasation (<1%)

[a] Pneumonia includes pneumonia and lung infection

[b] Sepsis includes sepsis, escherichia sepsis, and septic shock

Selected Other Adverse Reactions

- Inflammatory-related conditions were reported in 3% of patients in LOTIS-2, including pericarditis, pneumonitis, pleuritis, and dermatitis.

Table 2 summarizes the laboratory abnormalities in LOTIS-2.

Table 2: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients with Relapsed or Refractory DLBCL Who Received ZYNLONTA in LOTIS-2

Laboratory Abnormality	ZYNLONTA[a]	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic		
Platelets decreased	58	17
Neutrophils decreased	52	30
Hemoglobin decreased	51	10[b]
Chemistry		
GGT increased	57	21
Glucose increased	48	8
AST increased	41	<1[b]
Albumin decreased	37	<1[b]
ALT increased	34	3

[a] The denominator used to calculate the rate varied from 143 to 145 based on the number of patients with a baseline value and at least one post-treatment value

[b] No Grade 4 adverse reactions occurred

Postmarketing Experience

The following adverse reactions have been identified during post approval use of ZYNLONTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: telangiectasia, blister, rash vesicular

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells. There are no available data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Animal reproductive or developmental toxicity studies were not conducted with loncastuximab tesirine-lpyl. The cytotoxic component of ZYNLONTA, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

Lactation

Risk Summary

There is no data on the presence of loncastuximab tesirine-lpyl or SG3199 in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ZYNLONTA and for 3 months after the last dose.

Females and Males of Reproductive Potential

ZYNLONTA can cause fetal harm when administered to pregnant women.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating ZYNLONTA.

Contraception

Females Advise women of reproductive potential to use effective contraception during treatment and for 10 months after the last dose.

Males Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during the treatment with ZYNLONTA and for 7 months after the last dose.

Infertility

Males Based on the results from animal studies, ZYNLONTA may impair fertility in males. The effects were not reversible in male cynomolgus monkeys during the 12-week drug-free period.

Pediatric Use

Safety and effectiveness of ZYNLONTA in pediatric patients have not been established.

Geriatric Use

Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 × ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions. ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST).

ADC THERAPEUTICS

References: 1. ZYNLONTA [package insert]. Murray Hill, NJ: ADC Therapeutics SA; 2022. **2.** Hartley JA. Antbody-drug conjugates (ADCs) delivering pyrrolobenzodiazepine (PBD) dimers for cancer therapy. *Expert Opin Biol Ther*. 2020;21(7):931-943.

CONTENTS

An Unclear Path: What's the Best Route After CAR-T Failure in B-Cell Lymphoma?

The majority of patients with aggressive B-cell lymphoma treated with chimeric antigen receptor (CAR) T-cell therapy will experience some disease response, but durable complete responses only occur in a minority of patients. The best salvage therapy after CAR T-cell therapy failure remains undefined.

Thomas G. Martin, MD

Saad Z. Usmani, MD, MBA, FACP

POINT | COUNTERPOINT

CAR-T Versus Bispecific Antibodies in Multiple Myeloma: Which Is the Better Option for Patients?

Thomas G. Martin, MD, and Saad Z. Usmani, MD, MBA, FACP, debate treatment with CAR T cells versus bispecific antibodies in relapsed/refractory multiple myeloma. **12**

GET TO KNOW

Chadi Nabhan, MD, MBA, FACP

Dr. Nabhan, host of The HemOnc Pulse, a podcast from *Blood Cancers Today* and the Society of Hematologic Oncology, hopes to put clinicians treating hematologic malignancies out of a job in five years with the help of precision medicine. **7**

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- New Clinical-Molecular Prognostic Model for MDS Improves Prognostic Accuracy

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CORRECTION December 2022 issue: The In Focus article, "Clinicians Tackle the Challenges of MCL," misattributed a journal article to Nitin Jain, MD. The article should be attributed to Preetesh Jain, MD, of the University of Texas MD Anderson Cancer Center.

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About the Society of Hematologic Oncology
The Society of Hematologic Oncology was established as a nonprofit corporation in 2012 with aims to promote worldwide research, education, prevention, clinical studies, and optimal patient care in all aspects of hematologic malignancies and related disorders. The Society's global network supports and is supported by members from more than 110 countries, who are leading the vital efforts to further treatments for those afflicted by these diseases.

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Associate Editor's Message

Laurie H. Sehn, MD, MPH
Associate Editor

How to Choose the Right Treatment When There Are So Many Options in DLBCL

For patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), a new challenge has emerged. Given the multitude of novel therapies recently approved, clinicians must consider how to best sequence the options in individual patients.

After years of limited choices for treatment in the relapsed/refractory setting, the availability of numerous effective novel agents is a welcome dilemma. Historically, autologous hematopoietic stem cell transplantation represented the primary curative option. Beyond that, management quickly became palliative. Single-agent or multiagent chemotherapy yielded poor outcomes, with few patients achieving durable benefit.

Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 has transformed management for relapsed/refractory disease. It was initially evaluated in patients who had received at least two prior lines of therapy, and results exceeded expectations compared with standard management. With more than five years of follow-up of the initial pivotal trials, it seems fair to conclude that CAR T-cell therapy can be curative in approximately one-third of select patients amenable to treatment. Subsequent phase III trials have also demonstrated improvement in event-free survival in the second-line setting in transplant-eligible high-risk patients with axicabtagene ciloleucel or lisocabtagene maraleucel compared with the standard approach of salvage therapy and transplantation. More recently, safety and efficacy of second-line CAR T-cell therapy has also been demonstrated in transplant-ineligible patients, leading to approvals in this setting. Thus, CAR T-cell therapy has altered the treatment algorithm for relapsed/refractory patients and would be considered a preferred option for approved indications in appropriate patients.

Beyond CAR T-cell therapy, since 2019, four additional novel therapy approaches have been approved for treating relapsed/refractory disease. Available options now include the CD79b-targeted antibody-drug conjugate polatuzumab vedotin combined with bendamustine and rituximab (pola-BR); the XPO1 inhibitor selinexor; the anti-CD19 monoclonal antibody tafasitamab combined with lenalidomide (TAFA-LEN); and, most recently, the antibody-drug conjugate targeting CD19, loncastuximab tesirine-lpyl. Pola-BR approval was based on a randomized, phase II trial in comparison with BR alone, whereas remaining agents were approved based on pivotal phase II data. As such, comparative data among these options are lacking. Cross-trial comparisons cannot easily be made due to variable patient eligibility criteria leading to different patient characteristics. Collectively, overall response rates (ORRs) range from 28% to 58%, with complete remission (CR) rates ranging between 10% and 40%. While some patients have achieved durable benefit, follow-up durations are too short to assess the curative potential of these novel agents.

Considerations for sequencing should take into account overall goals of therapy, assessment of risk and benefit in individual patients based on unique toxicity profiles, and patient preferences. While pola-BR was evaluated in relapsed/refractory patients who had received at least one prior line of therapy, the U.S. Food and Drug Administration indication is for patients following two prior lines (despite broader indication worldwide). In the randomized cohort of the phase II trial, the ORR was 45% (CR rate, 40%), and median progression-free survival (PFS) and overall survival (OS) were 9.2 months and 12.4 months, respectively. Advantages of pola-BR include the fact that it is a finite regimen (intended for six cycles) and is generally well tolerated. Primary toxicities include cytopenia and neuropathy. Due to profound lymphodepletion, bendamustine should be avoided prior to CAR T-cell therapy.

TAFA-LEN, a novel immunotherapy approved for use after one prior line of therapy, has shown durable benefit in patients achieving a CR. In the phase II trial, the ORR was 58% (CR rate, 40%), and median PFS and OS were 11.6 months and 33.5 months, respectively. The treatment does require frequent intravenous infusion of tafasitamab, which continues indefinitely, whereas lenalidomide is limited to a duration of one year. This regimen has been attractive, as it avoids the use of further chemotherapy, but it is not without toxicity, which is largely attributable to lenalidomide. Limited data suggest that CD19 downregulation following tafasitamab is not a major concern, but it should remain a consideration when sequencing prior to CAR T-cell therapy. Of note, the pivotal trial was performed in a favorable patient cohort, as primary refractory patients were initially excluded. A recent real-world analysis suggests this regimen is most effective in patients with relapsed disease following one prior line of therapy.

Selinexor, an oral agent taken twice weekly until progression, has been approved after two lines of prior therapy. In the phase II trial, the ORR was 28% (CR rate, 10%), and median PFS and OS were 2.6 months and not yet reached, respectively. Primary toxicities include constitutional symptoms and fatigue that may impact quality of life. Selinexor offers a convenient schedule of administration, but modest activity has lowered enthusiasm for its use.

Finally, loncastuximab tesirine-lpyl, administered intravenously every three weeks for one year and every three months subsequently, has also been approved following two lines of therapy. In the phase II trial, the ORR was 48% (CR rate, 24%), and median PFS and OS were 4.9 months and 9.9 months, respectively. It is generally well tolerated, with main toxicities including cytopenia and transient transaminitis. Initial reported activity appears modest, but longer follow-up and more data in earlier lines of therapy would help judge its merit. Also, few data are available regarding its use prior to CAR T-cell therapy, which is a consideration based on its CD19 target.

The expected approval of bispecific antibodies in patients who have received at least two prior lines of therapy will likely make management in the relapsed/refractory setting increasingly complex. Bispecific antibodies, such as glofitamab, epcoritamab, and odronextamab, have shown the ability to induce durable remissions following multiple lines of therapy, including CAR T-cell therapy. Based on their reported efficacy and favorable toxicity profile, bispecific antibodies will likely be highly utilized and may be prioritized ahead of several current available options.

For an in-depth look at how clinicians are strategizing B-cell lymphoma treatment, read this issue's feature on page 9.

The availability of an array of novel therapies in relapsed/refractory DLBCL has undoubtedly improved outcomes. However, more information is required to optimize their use. In view of the biological diversity of DLBCL and the variable resistance mechanisms that may be at play in individual patients, identifying predictive biomarkers is a high priority. Ultimately, the availability of validated biomarkers is essential to move from the current approach of empiric therapy toward precision-based care.

Laurie H. Sehn, MD, MPH, *is a Clinical Professor of Medical Oncology at the British Columbia Cancer Centre for Lymphoid Cancer.*

Calendar

March 2–3
American Society of Hematology Summit on Immunotherapies for Hematologic Diseases
Omni Shoreham Hotel
Washington, DC

March 31–April 2
National Comprehensive Cancer Network 2023 Annual Conference
Orlando World Center Marriott
Orlando, Florida

April 14–19
American Association for Cancer Research Annual Meeting 2023
Orange County Convention Center
Orlando, Florida

April 21–22
20th Annual International Ultmann Chicago Lymphoma Symposium
Westin Chicago River North
Chicago, Illinois

April 23–26
49th Annual Meeting of the European Society for Blood and Marrow Transplantation
Paris Congress Centre
Paris, France

April 27–29
International Summit on Hematology and Blood Disorders
Hilton Garden Inn Lake Buena Vista/Orlando
Orlando, Florida

May 3–6
17th International Congress on Myelodysplastic Syndromes
Marseille Chanot Convention Center
Marseille, France

May 10–13
American Society of Pediatric Hematology/Oncology Conference
Fort Worth Convention Center
Fort Worth, Texas

May 12–13
Turkish Society of Hematology 9th International Congress on Leukemia, Lymphoma, Myeloma
Virtual event

June 2–6
American Society of Clinical Oncology Annual Meeting
McCormick Place
Chicago, Illinois

June 8–11
European Hematology Association Hybrid Congress
Messe Frankfurt
Frankfurt, Germany

June 13–17
17th International Conference on Malignant Lymphoma
Palazzo dei Congressi
Lugano, Switzerland

July 27–29
32nd Annual Mayo Clinic Hematology/Oncology Reviews 2023
The Ritz-Carlton Amelia Island
Amelia Island, Florida

MARK YOUR CALENDARS
SEPTEMBER 6–9
2023 SOHO Annual Meeting
George R. Brown Convention Center
Houston, Texas

Get to Know

Learn more about the leaders, innovators, and educators in hematologic oncology

Chadi Nabhan, MD, MBA, FACP

Dr. Nabhan, a hematologist and medical oncologist and the host of The HemOnc Pulse, a podcast from *Blood Cancers Today* and the Society of Hematologic Oncology, hopes to put clinicians treating hematologic malignancies out of a job in five years with the help of precision medicine.

What led you to pursue a career in medicine?
I never thought I was going to be in medicine. I grew up thinking I was going to be a journalist. I've always enjoyed journalism, but I wanted to be an investigative journalist or one who authors a story that has a significant impact on policy and politics.

I grew up in Syria, and I did very well in high school. My dad said, "Well, you should apply to medical school because it's very competitive. You can still do journalism on the side as a hobby." I did, and I started loving it. I started loving the human connection of things.

Stories are the link between journalism and medicine. Every patient you interact with has a story. All of us are going to be patients at some point, if we haven't been already, so we all have these stories. It's about the human connection with people and being able to understand what they went through. Frankly, there is nothing more honorable than someone trusting you at their most vulnerable time in life. The human connection and the impact on patient lives are what led me to pursue medicine as a career in the end.

"Stories are the link between journalism and medicine. Every patient you interact with has a story. All of us are going to be patients at some point, if we haven't been already, so we all have these stories. It's about the human connection with people and being able to understand what they went through."

You're prominent on social media, you've written a book, and you host several podcasts. What led you to work in scientific and medical communications?
Social media really started as a hobby. The reason I joined Twitter was because I was on the board of a not-for-profit organization for patients called the Double Hit Lymphoma Foundation. The foundation was created by the wife of a patient who was diagnosed with this disease, and I joined the board of that organization. She told me I must join Twitter because I can help educate people about the foundation and disease, and potentially I can help raise funds that could be dispersed to help patients diagnosed with this illness. That was the reason I originally joined social media. Then I realized that there are a lot of people on social media who are like-minded, who I could learn from and have a conversation with about medical topics.

I started enjoying the community I was building around me and getting to meet people who I otherwise wouldn't have met because you're always limited by where you work and geography. But social media really breaks all those barriers, and suddenly you could be communicating with someone who lives in Japan and collaborating with someone who lives in Europe. That is what attracted me to the social media component. I started doing podcasts in February 2019. I chose topics that would be helpful to listeners and mainly focused on medical topics of relevance. I view myself as almost a reporter when I'm doing the podcast. I try to report the facts, what's happening in the medical community, and what's on the minds of people who are in the medical circle.

Can you talk about the launch of The HemOnc Pulse?
This is a new podcast that I have the privilege of hosting. We wanted to create a podcast dedicated to the world of hematologic oncology, which has become complex when it comes to the type of diseases that physicians are dealing with and the therapeutics that are required to be used or that physicians need to be aware of. There are other elements of hematology that are important from a health care policy perspective. How do you manage coordination of care with complex therapies like CAR T cells, how do you navigate drug prices, and how do you make care more affordable to patients?

We named it The HemOnc Pulse because I envisioned that this podcast will be how physicians, students, fellows, residents, patients, families, researchers, investigators—everybody—can keep their fingers on the pulse of what's happening in the world of hematologic oncology.

How do podcasts and social media help deliver the information clinicians need?
It goes without saying that the world of hematologic oncology has become complex. How do you keep up with all the information that is coming out? Ultimately, there are patients you care about, and you want to make sure you are up to date with all the information you need to help them. People consume information in different ways. You may, for example, like to watch a TV show or webinar. Some people like to read a book, and others like to listen to an audiobook. Some people like to do both, depending on what they're doing (if they're busy, they're driving, and so on).

This podcast is for folks who prefer to consume information by listening. We spend a lot of our time flying, walking, and driving. A lot of the time you just want to listen to music or something fun, but every so often, you try to make better use of your time. You want to listen to something more educational. Hopefully, if you are in that mood, you think about this podcast and click on it.

Also, we're going to solicit feedback on the podcast. Our goal is to refine it to be aligned with what our stakeholders expect of us.

What do you most hope that listeners take away from your podcasts?
I say if you listen to the podcast and you leave knowing more than when you started listening, then the podcast is successful. Even if it's one piece of information. You start listening, and by the time you finish, you learned a couple of things that you did not know. Then, to me, the podcast is successful.

You were an author on a recent paper titled "Recognizing Unmet Need in the Era of Targeted Therapy for CLL/SLL: 'What's Past Is Prologue.'" Can you speak to those unmet needs and some potential solutions or continued challenges you see in the future?
This paper was written by many of my colleagues in the world of lymphoma and chronic lymphocytic leukemia (CLL). It was spearheaded by Dr. Anthony Mato, who is the first author of this paper. The goal was to identify the issues we are dealing with in this entity and define

Get to Know

how we can move the field forward. We recognized that there are several aspects of managing patients with CLL that are challenging. Take patients who have failed targeted therapies as an example. There are several targeted therapies currently available for the treatment of CLL. We don't know right now what we can do for patients who have failed these therapies, or who have developed toxicities to these target therapies that preclude us from continuing the use of this treatment.

This is an unmet need. What do you do for this cohort of patients? If you are a manufacturer looking at the field of CLL, we would urge you to look at that space. We prefer that you dedicate resources to the patients who are losing treatment options versus going up against existing treatment options, unless you are competing based on fewer side effects or cheaper drugs.

What are the major financial challenges in the treatment of hematologic malignancies? How can the public-private sector work together to address these challenges?

I'll start with the second question first. They must work together. The idea that one entity can work on its own to improve the outcomes of patients with cancer is completely unrealistic, and I think it is shortsighted. We all need to work together to improve the outcomes of patients. The challenges of hematologic malignancies are multiple, but it is important to look at the cost of therapy. It is important to try to understand the affordability of treatment. If there are therapies that are very effective but patients cannot take these treatments because they are too expensive, patients will not benefit. Part of this is we have to look at the cost.

The other piece that I think is important, as many treatments are becoming oral therapies, is what measures can we implement to improve the adherence to oral therapies? It is not always easy to adhere to the treatment. I think we must create metrics to make sure that the patients adhere to it.

The third piece is logistics. Some of these treatments are complex and require inpatient treatment, outpatient treatment, or treatment in clinic and outside of clinic. Navigating a complex health care system is difficult.

You are largely focused on precision medicine in your research and your work. How did you become interested in precision medicine?

We've always thought the most important or the easiest way to define precision medicine is treating the right patient with the right drug at the right time. This is precision medicine. If you think about it, this is what doctors do all the time. It's not like we treat patients randomly. We treat patients with the right drug at the right time. What has changed is that we understand the disease better now. We understand what drives the disease much better than before. We understand the molecular underpinning of the disease and what is really making the cancer grow, what is making the cancer cells behave differently than normal cells. By knowing these things, you can be smarter and more effective in designing a treatment against that type of disease.

You're still treating the right patient with the right drug at the right time, but what has changed is that you know more about how to treat, when to treat, and why to treat. Precision medicine, in my view, implies deeper and better understanding of the actual cancer and what drives it. Precision medicine is about knowing the foundation of that cancer.

What are your biggest hopes for precision medicine as it relates to hematologic malignancies over the next five years?

I want all doctors treating hematologic malignancies to be unemployed. My goal is to hopefully put them all out of a job. We cure all hematologic malignancies, and they can go golfing and fishing. Is it feasible? I don't think so. I think that might be wishful thinking, but I do think we will be able to make patients live longer and better. That is the ultimate challenge. What can we do together as a community so that patients live longer and better? Because it's not about the quantity of life, it is also about the quality of life. If we're able to do that, then we have succeeded as a community. We all need to work on that goal together.

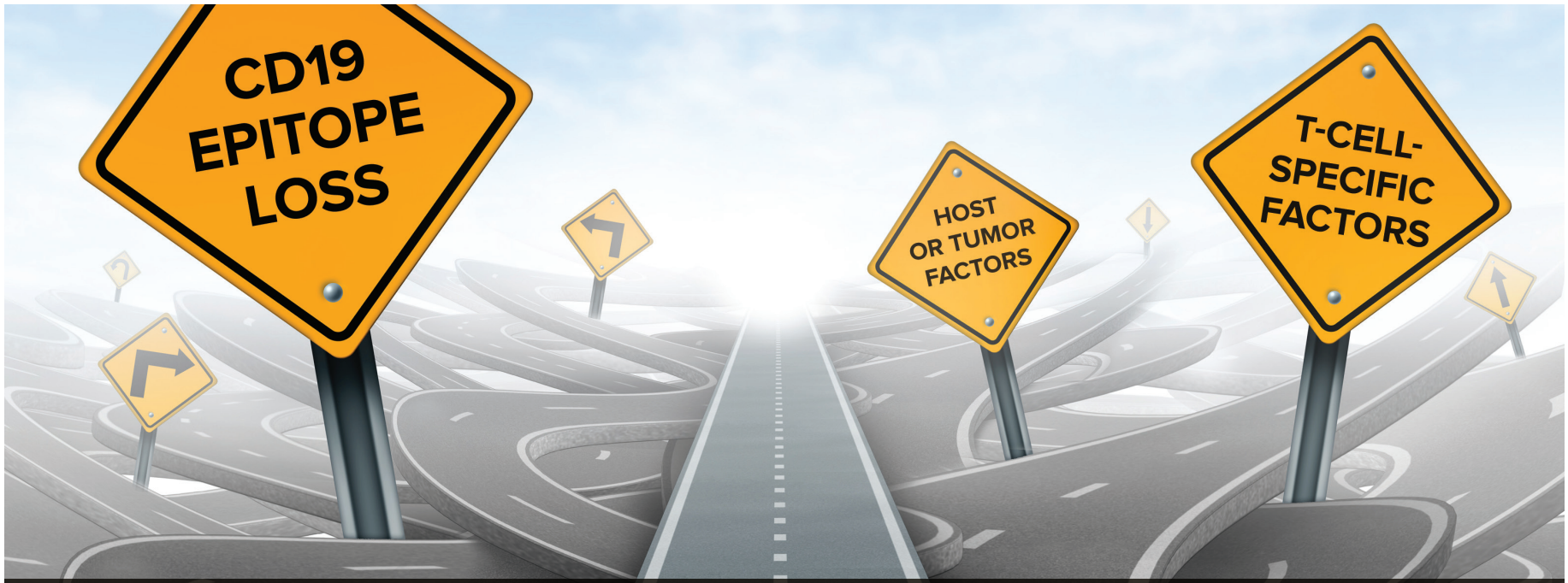
What do you do in your free time?

My passion is to write, and I love to read. I used to read a little bit more, but time has been difficult. I like to get through one book a month. I think for avid readers that's probably not a lot. My goal has always been 12 to 15 books a year. I think the more you read, the better you write. So, my passion is reading, writing, and (of course!) podcasting.

Is there anything we haven't talked about that you'd like to tell our readers?

Be sure to check out The HemOnc Pulse. I think it's going to be well worth their time, and I look forward to hearing their feedback and what we could do better to accommodate their expectations.

Chadi Nabhan, MD, MBA, FACP, *is a hematologist and medical oncologist and the host of The HemOnc Pulse, a podcast from* Blood Cancers Today *and SOHO. You can follow him on twitter @chadinabhan. Dr. Nabhan is also the creator and host of the podcast "Healthcare Unfiltered" and the author of* Toxic Exposure: The True Story behind the Monsanto Trials and the Search for Justice. *He serves on the editorial board for* JAMA Oncology.



An Unclear Path: What's the Best Route After CAR-T Failure in B-Cell Lymphoma?

The majority of patients with aggressive B-cell lymphoma treated with chimeric antigen receptor (CAR) T-cell therapy will experience some disease response, but durable complete responses (CRs) wonly occur in a minority of patients.

"If you look at outcomes, we are potentially curing about one-third of patients [with CAR-T]," said **Kami J. Maddocks, MD,** Professor of Clinical Internal Medicine in the Division of Hematology at the Ohio State University Wexner Medical Center. "That leaves about two-thirds of patients who don't respond to CAR T-cell therapy or [who] initially get a response but later progress."

Outcomes in patients who progress or relapse after undergoing CAR T-cell therapy are poor. A recent analysis of the French registry DESCAR-T looked at outcomes from 550 patients with aggressive B-cell lymphomas who experienced progression or relapse after CAR T-cell therapy. Median progression-free survival (PFS) was 2.8 months, and median overall survival (OS) was 5.2 months. Patients who relapsed or progressed within 30 days had a median OS of 1.7 months.[1]

These poor outcomes emphasize the need for dedicated treatment strategies in this patient population. Unfortunately, there are currently no real standards of care in place, Dr. Maddocks said.

Indeed, picking the best strategy and knowing how to sequence available therapies can be very challenging, noted **Iris Isufi, MD,** Associate Professor of Medicine at the Yale School of Medicine and Co-Director of the Adult CAR T-Cell Therapy Program at the Yale Cancer Center.

"The decision can really be crucial because that may be the only chance the patient gets," Dr. Isufi said. "If they miss that chance, the majority die of disease progression."

CAR T-Cell Treatment, Failure

There are currently several U.S. Food and Drug Administration (FDA)-approved CAR T-cell therapies for relapsed or refractory large B-cell lymphomas. Lisocabtagene maraleucel is approved after two or more lines of therapy for diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and certain follicular lymphomas (FLs). Tisagenlecleucel is approved for relapsed or refractory DLBCL. Axicabtagene ciloleucel is approved after two or more lines of therapy for DLBCL, primary mediastinal B-cell lymphoma, high-grade DLBCL after FL, and FL.

More recently, axicabtagene ciloleucel was also approved for large B-cell lymphoma refractory to first-line chemoimmunotherapy or disease that relapses within 12 months of first-line chemoimmunotherapy.[2]

Disease response and durability vary slightly across these different therapies and across disease subtypes, Dr. Isufi said, but approximately 35% to 40% of patients are long-term survivors.

"This is in comparison to the pre-CAR T cell era where probably fewer than 10% were long-term survivors and survived beyond six months," Dr. Isufi said.

Certain factors seem to be associated with failure after CAR T-cell therapy, according to Dr. Isufi. A 2019 review paper broke these factors down into three categories: tumor-intrinsic factors, host factors, and inadequacies of CAR T cells.[3]

Several studies have shown that "about one-third of patients will have loss of CD19 expression at disease progression," Dr. Maddocks said.[4,5]

Host-related factors include presence of bulky disease, poor performance status, high inflammatory markers, and elevated lactase dehydrogenase. Resistance to CAR T-cell therapy may also be associated with tumor and systemic immune dysregulation.[6]

However, none of these factors are universal, Dr. Maddocks noted. "Patients with these characteristics are at high risk for not responding, but we have seen patients with low tumor burden going in who end up progressing," she said.

Use this QR code to hear more about this topic from lymphoma experts in a roundtable discussion moderated by Kami J. Maddocks, MD.

The time of relapse can also be meaningful, Dr. Isufi said. The analysis of the DESCAR-T registry grouped patients into very early (day 0-30), early (day 31-90), and late (day 90) relapse categories. Less than 20% of patients who had very early relapse were alive at six months, and very early progression was associated with worse OS from time of relapse/progression on multivariable analysis.[1]

Treatment Options

"There is no established first-line treatment after CAR T-cell therapy failure for aggressive B-cell lymphomas," Dr. Isufi said. "The decision-making for these patients is very much physician-dependent and

influenced by patient factors."

Prior to undergoing CD19-targeting CAR T-cell therapy, most patients will not have received other CD19-directed therapies, according to **Craig Sauter, MD,** Director of the Blood and Marrow Transplant Program at the Cleveland Clinic.

Loncastuximab tesirine-lpyl is a CD19-directed antibody and alkylating agent conjugate approved for patients with DLBCL with two or more prior lines of therapy.[7] Data from the LOTIS-2 trial showed an overall response rate (ORR) of 48.3%. A small study has shown that loncastuximab may be an option for patients who have relapsed after CAR T-cell therapy.[8]

Another CD19-directed option is the cytolytic antibody tafasitamab-cxix given in combination with lenalidomide. The FDA approved tafasitamab for patients with relapsed or refractory DLBCL who are not eligible for autologous hematopoietic stem cell transplant.[9] Long-term data from the L-MIND study of tafasitamab showed an objective response rate of 57.5% among patients with one to three prior therapies, with a median duration of response of 43.9 months.[10]

"I would consider loncastuximab or tafasitamab and lenalidomide in patients who still have CD19-positivity after CAR-T failure," Dr. Isufi said.

However, Dr. Sauter pointed to the presentation of "sobering" results from a real-world trial of the tafasitamab and lenalidomide combination at the 2022 American Society of Hematology Annual Meeting and Exposition that showed that clinical outcomes in terms of response and survival were lower than what was seen in the L-MIND clinical trial.[11] More than 90% of patients in this real-world study did not meet the criteria for the L-MIND study. However, the study did show that prior CAR-T or other CD19-directed therapy were not associated with worse outcomes.

"I suspect this combination regimen was difficult to give, potentially because of blood count issues and rapidly growing disease," Dr. Sauter said.

Prolonged cytopenia is often an issue in patients after undergoing CAR T-cell therapy and may limit salvage treatment options.

For example, the CD79b-directed antibody-drug conjugate polatuzumab vedotin-piiq is approved in combination with bendamustine and rituximab in patients with DLBCL with two prior lines of therapy.[12] In the trial leading to regulatory approval, the objective response rate was 45%.

However, Dr. Isufi pointed out that it is challenging to give a triplet after CAR T-cell therapy failure due to increased risk for cytopenia.

"A majority of patients may only tolerate polatuzumab with rituximab," Dr. Isufi said.

Despite the risk of cytopenia, Dr. Sauter added that in some patients who have aggressive disease, clinicians may prioritize the perceived speed of response gained with chemotherapy as opposed to more novel or "gentle" agents like lenalidomide or ibrutinib.

For patients who receive CAR T-cell therapy in the second line and progress, exposure to a platinum-containing salvage regimen may be the best option, Dr. Sauter said.

"Platinum-based salvage programs were generally developed for patients eligible to proceed to transplant," he noted. "Whether or not these patients who get CAR-T in the second line should go on to a platinum agent and go to transplant is a wide-open question."

Additional Options

Because T-cell exhaustion and an immunosuppressive tumor microenvironment can both be possible causes of CAR T-cell therapy failure, research has also explored the use of immune checkpoint inhibitors as a salvage therapy.

"The rationale for administering checkpoint inhibitors makes sense," Dr. Sauter said. "There was early correlative experience that exhaustion markers are upregulated after infusion."

"The thought was that you could reinvigorate the CAR T cells," added **Natalie Grover, MD,** Clinical Director of the Cellular Therapy Program at the University of North Carolina Lineberger Comprehensive Cancer Center.

One small study of patients with B-cell lymphomas who were refractory or relapsed after CD19-directed CAR T-cell therapy treated them with pembrolizumab and showed a best ORR of 25%.[13]

"Initially, the data were promising, but it hasn't seemed so more recently," Dr. Grover said. "Some clinicians may go that route post-CAR T-cell therapy, but I generally haven't been."

Another option that could be used is selinexor, a first-in-class oral selective inhibitor of nuclear export compound, in combination with bortezomib and dexamethasone. The FDA approved this combination in June 2020 for patients with relapsed or refractory DLBCL who have had two or more prior lines of therapy.[14] Results of the SADAL trial, which led to regulatory approval, showed an ORR of 29%, with a CR rate in 13% of patients.[15]

However, Drs. Grover and Sauter said they do not see this therapy used often in the post-CAR T-cell setting. More often it is used in patients who are not candidates for CAR T-cell therapy or as bridging therapy.

Dr. Grover said that for some patients experiencing local relapse, radiation may be a consideration.

"A lot of times patients who relapse post-CAR T-cell therapy will have a lot of cytopenia," Dr. Grover said. "These patients are tired and deconditioned from other prior treatments. In specific cases, if the disease is amenable, I might try radiation to give the patient a break from those more intensive therapies."

As with other treatment options, limited data exist for the use of radiation as a salvage strategy post-CAR T-cell therapy. One small study looked at 14 patients treated with salvage radiation to sites previously positron emission tomography-avid prior to CAR T-cell infusion. The median OS after radiation was 10 months. Six of 14 patients achieved 100% response, and three patients were bridged to allogeneic transplant.[16]

Finally, there may be some patients for whom palliative treatments are the best next step.

"In general, the prognosis is poor once a patient progresses after CAR T-cell therapy," Dr. Grover said. "Some of these patients may have exhausted a lot of options prior to CAR-T. They may be CD19-negative, and already exposed to polatuzumab, be chemo-refractory, frail, or have really explosive disease. At that point, palliative options warrant a conversation."

Future Hope

In addition to these approved options, clinicians are hopeful that T-cell-engaging bispecific antibodies may prove to be an effective option for patients who relapse after CAR T-cell therapy.

Glofitamab, a CD20×CD3 bispecific monoclonal antibody, was evaluated in a phase II study of patients with relapsed or refractory DLBCL, about one-third of whom had received prior CAR T-cell therapy. The CR rate was 35% among the group with prior CAR-T.[17]

Epcoritamab, another bispecific antibody, was also evaluated in patients with relapsed or refractory DLBCL, approximately 39% of whom had received prior CAR T-cell therapy. The ORR among all patients was 69%. It was 54% among those with prior CAR-T, with 34% of patients achieving CR.[18] Glofitamab and epcoritamab are both currently under priority review with the FDA.[19,20]

"If I have a patient who is eligible for a trial of a bispecific antibody, I try to prioritize that option for these patients," Dr. Maddocks said.

Dr. Grover agreed: "Once these get approved, they will be a potential first choice that I go to post-CAR-T relapse."

More Research Needed

Dr. Sauter emphasized that there is often no clear choice for the best salvage treatment option in patients who are refractory to or have relapsed after CAR T-cell therapy. Retrospective studies attempting to identify superior approaches have had inconclusive results.

Two recent studies have indicated that responses may be better with novel therapies. One study summarizing outcomes of the first therapy given after CD19-directed CAR T-cell treatment failure showed that 74% of patients received some kind of subsequent anti-cancer treatment, most commonly polatuzumab-, standard chemotherapy-, or lenalidomide-based. No CRs were achieved with conventional chemotherapy. CR rates greater than 30% were seen with polatuzumab- or lenalidomide-based therapies. The presence of two or more risk factors—bulky disease, lack of CAR T-cell response, age greater than 65 years, or elevated lactate dehydrogenase—was associated with inferior survival.[21]

Results of a study out of Spain also indicated that salvage treatment with novel agents may be better than standard chemotherapy in regard to response rates, but survival differences were not addressed.[22]

Another retrospective study assessing factors associated with response to salvage therapy confirmed better responses among patients who had initially responded to CAR T-cell therapy compared with non-responders. However, when comparing lenalidomide-based regimens, Bruton's tyrosine kinase inhibitors, checkpoint inhibitors, chemoimmunotherapy, allogeneic transplantation, and other options, there was no significant difference in OS based on the type of salvage regimen used.[23]

"It is a real conundrum," Dr. Sauter said. "The need for prospective evaluation of interventions is a large unmet need."

Even when bispecific antibodies are ultimately approved, how these drugs are sequenced in relation to CAR T-cell therapy will need to be evaluated.

Dr. Sauter also said that it is surprising that more research has not been done into whether a second infusion of CD19-targeted CAR T cells is a valid salvage approach.

One single-institution study looked at a second CD19 CAR T-cell infusion in B-cell malignancies, including leukemias, in patients who had evidence of

persistent or relapsed disease 21 days or more after the first infusion. With the second infusion, complete remission was achieved in 19% of patients with non-Hodgkin lymphoma. Higher ORRs and longer PFS after the second infusion were associated with the addition of fludarabine to cyclophosphamide-based lymphodepletion before the first CAR T-cell infusion and an increase in the dose at the second infusion compared with the first infusion.[24]

"When cellular therapies were developed for viral-mediated disease following allogeneic transplant in other settings, a lot of strategies looked at multiple infusions," Dr. Sauter said. "In cancer, we often give therapies in cycles, so it is curious that there has not been more of an investigational pursuit."

Dr. Sauter is currently involved in the Southwest Oncology Group's 2114 trial, a phase II study that will evaluate whether the bispecific antibody mosunetuzumab-axgb and/or polatuzumab vedotin benefits patients who have received prior chemotherapy followed by CAR T-cell therapy.[25]

"We are hoping to enroll at least 30 patients on each arm, so this will be a large study," Dr. Sauter said. "The study is for patients [who] have stable disease or partial remission at day 30 after CAR to see if we can deepen response and improve PFS as a primary endpoint."

Patients will be assigned to observation, mosunetuzumab, polatuzumab vedotin, or a combination of the two. At the time of publication, the trial was not yet recruiting.

Dr. Maddocks agreed that clinical trials are needed and can be an option for this patient population, but she added that the practicalities of enrolling these patients are complicated.

"These patients often have low blood counts, rapidly progressing disease, or have received a lot of prior therapies," Dr. Maddocks said. "That often makes it difficult."

In fact, a study looking at barriers to enrollment in clinical trials after post-CAR T-cell therapy disease progression found that approximately half of patients would be excluded from landmark clinical trials looking at salvage treatments, most commonly because of hematologic exclusion criteria.[26]

As the field moves forward, more post-CAR T-cell therapy salvage regimen research may be done in patients who undergo CAR T-cell infusion as a second-line option.

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CAR-T Versus Bispecific Antibodies in Multiple Myeloma: Which Is the Better Option for Patients?

Thomas G. Martin, MD, Associate Director of the Myeloma Program at the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, and **Saad Z. Usmani, MD, MBA, FACP,** Chief of the Myeloma Service at the Memorial Sloan Kettering Cancer Center, debate treatment with chimeric antigen receptor (CAR) T cells versus bispecific antibodies in relapsed/refractory multiple myeloma (MM).

CAR T-Cell Therapy: Best Option for Patients

By Dr. Martin


Thomas G. Martin, MD

The topic is CAR T-cell therapy versus bispecifics and which is the best option for patients. That's an easy question for me to answer and let me tell you why. In the current treatment paradigm for patients with myeloma, they receive induction therapy followed by autologous transplant, for those who are eligible, and then everyone gets maintenance. It's a continuous treatment model. Once relapse occurs, patients receive multiple regimens, class-switching agents with each subsequent relapse, and again patients continue treatment until progression. Eventually, patients are multiply relapsed or refractory, and this is the point where we're now testing CAR T-cell therapies and bispecifics.

Both therapies have shown deep and durable responses in refractory patients, which are responses that we have never seen before. There is excitement for both CAR and bispecifics.

What is the best therapy option? Well, in fact, the best option for any individual patient requires a discussion between the doctor and patient. The fact that CAR T-cell therapy has been associated with an overall response rate (ORR) of 98% (CARTITUDE study) and is considered a "one-and-done" strategy—meaning that after CAR therapy, the patient gets to enjoy an "off" treatment period—typically has swayed the patient to CAR T-cell therapy.

I'll digress and tell you that my first true "excitement" for CAR therapy in MM developed back in 2017 at the American Society of Clinical Oncology (ASCO) Annual Meeting, where we heard a presentation from Legend Biotech, a small company from China. They reported on 19 patients with relapsed/refractory MM treated with a B-cell maturation antigen (BCMA) CAR T-cell therapy. The ORR was 100%, quite impressive, and even patients with extramedullary disease had a response. After ASCO, one of the scientists from Legend came to our institution and asked if we would be interested in helping with development in the United States (of course).

A week later, a patient asked—and he was serious—if he could "get that CAR in China." This was a triple-class refractory patient for whom we had run out of options. So, we asked Legend if we could send over a patient, and the answer was yes.

Thus, there was one patient from the United States treated on that LEGEND study in 2018 in China. Again, this patient was triple-class refractory with extramedullary disease (multiple plasmacytomas in the mouth). He left for China and was there for just over three months. When he came back, he was in complete remission and was minimal residual disease (MRD)-negative. That was a true turning point for me. Since then, I have favored the amazing responses from CAR T-cell therapy.

Now, many CAR studies have been reported, with generally positive data. The phase II KarMMa study, reported in *The New England Journal of Medicine* in February 2021, included patients with relapsed/refractory MM who were heavily pretreated and showed an ORR of 73%, and 26% of all patients achieved MRD negativity. The progression-free survival (PFS) in those receiving the highest dose of idecabtagene vicleucel (ide-cel) was about 12 months, and this study led to U.S. Food and Drug Administration approval of ide-cel. Two additional things I'll point out: 35% of patients had high-risk cytogenetics, and 39% had extramedullary disease. Those are very impressive results for ide-cel in relapsed/refractory MM.

The second approved CAR-T therapy, ciltacabtagene autoleucel (cilta-cel), was approved based on the phase I/II CARTITUDE study. This study involved 97 patients with relapsed/refractory MM, 13% with extramedullary disease, 24% with high-risk cytogenetics, 88% triple-class refractory, and 99% refractory to their latest line of therapy. It showed an ORR of 98%. Of interest, the cilta-cel CAR contains two BCMA-binding domains, which may make a better immunologic synapse and may be responsible for such a high response rate. Follow-up data reported at ASCO in 2022 showed a PFS rate of approximately 57% at 27 months of follow-up, which is the longest PFS reported in this setting. Of note, this is 27 months off therapy!

We also need to consider the toxicities from each treatment. The two most common side effects after CAR therapy are cytokine release syndrome (CRS) and hematologic toxicity. CRS generally occurs within days to the first week or two and is seen in approximately 80% to 95% of patients. It's generally grade 1-2, manageable, and resolves within three to four days of onset. We are very liberal with our use of tocilizumab (with first fever no matter the grade of CRS), and this has worked well. Cytopenia is also common and is a result of the fludarabine and cyclophosphamide chemotherapy and the cytokine storm from CRS. Grade 3/4 neutropenia, thrombocytopenia is common, as well as anemia. These side effects are also manageable and reversible, but they may be prolonged.

Neurologic toxicity is managed with steroids and is generally reversible. Specifically, with cilta-cel, late neurotoxicity can occur, including Parkinsonian-like symptoms and cranial neuropathies. These side effects occur approximately 10% of the time. Since CARTITUDE-1, the cilta-cel program mandated mitigation strategies, including prompt treatment of CRS and appropriate use of bridging chemotherapy to debulk the disease before CAR, and only one case of late neurotoxicity has been seen out of 200 cilta-cel patients.

> **"We are going to have so many ways to innovate with CARs, and the next generation of CARs will even be better."**
>
> *—Thomas G. Martin, MD*

Overall, the toxicity from CAR therapy is very manageable, and the biggest concerns from patients are access (there are not enough CAR slots for the demand, and too many patients are waiting) and logistics. It is very difficult for some patients to relocate to the CAR T-cell center for approximately one month. Bispecifics are easier to give because they are "off the shelf," but they do require an inpatient stay, as the first few doses are also associated with CRS. We use tocilizumab to turn off CRS with bispecifics just like we do for CAR. So, the hospital stay is shorter, but bispecifics are not "one and done." They require continuous therapy. Emerging data suggest that the continuous suppression of B cells with BCMA-directed bispecifics may be associated with greater infection risk. So, the benefit of being off therapy is a real "winner" and drives patients' choices.

Cost is certainly an issue, and both therapies are expensive. However, if the median PFS for cilta-cel is 27 months, then the monthly cost is actually less than $18,000, which is approximately the cost of one month of lenalidomide maintenance. To put the nail in the coffin (so to speak), we are going to have so many ways to innovate with CARs, and the next generation of CARs will even be better. I think responses will be more durable, and patients won't even have to be hospitalized for CAR therapy. It's an easy choice: CAR, CAR, CAR.

Bispecifics Will Overtake CAR T Cells in Myeloma Treatment

By Dr. Usmani

Saad Z. Usmani, MD, MBA, FACP

The stance I have been asked to take is that bispecific antibodies will beat CAR T-cell therapies in MM, a very hot topic.

It's not a matter of how but when the bispecifics will take a pole position in how we are managing MM out in the community. As a transplant cellular therapy doctor, I'm very comfortable saying that, because that's where the care will eventually head. This will be a challenge we will have to accept, because we are still going to be developing cellular therapies for our patients. Why do I say that? Because there is a lot of promise to this T-cell redirection strategy, and CAR T-cell therapies have been very promising.

But bispecifics also give very high response rates. We're still waiting for those CAR T-cell promises. We had the ide-cel approval that came in the spring of 2020. We had the cilta-cel approval that came in 2021. But the number of patients waiting for CAR T-cell therapy has not decreased. If anything, it's compounded. This is a challenge for us, the transplant therapy doctors who are communicating with community physicians and managing those patients out in the community. Trying to get a CAR T-cell slot is a major challenge. We are still waiting for those promises to be delivered. To make the statement that CAR-T is a "one-and-done" strategy? Well, yes, until it's not. We have to wait for our pharma colleagues to work this out and increase capacity. Get good quality products to us so we can say that those CAR-T promises are coming true and coming to fruition.

In this case, why wait for CAR T cells when bispecifics can get the job done, and perhaps even better than CAR T-cell therapy in terms of the safety profile? One of my patients had about 15 lines of treatment before he went on a BCMA-directed bispecific antibody in the summer of 2019. The patient came off after eight cycles because he had a propensity for pneumonias and upper respiratory tract infections and was admitted to the hospital with pneumonia right before COVID-19 was about to hit. That was two and a half years ago. The patient is still off therapy and MRD-negative by next-generation sequencing as well as flow. He's never been off of therapy during his whole 20-plus years of myeloma survivorship.

If bispecifics can get you there, that's your one and done. The advantage with bispecifics is you have many different platforms. You have the option of potentially modulating CRS by giving therapies at different frequencies and schedules. This is what a lot of companies are exploring right now. This is a major advantage compared with CAR T-cell therapies. We have CAR T-cell therapies targeting BCMA. The bottom line is all these bispecific therapies are giving you response rates well over 60%.

What CAR T-cell therapy data don't tell you is the number of patients who were planned for apheresis or planned to get CAR T-cell therapy but never made it there. The total ORRs you see are for patients who got the CAR T-cell therapy. But if you change the denominator to the intended patient population, that number will dwindle. You get the impressive numbers with these bispecifics. You see ORRs are very high, 60% to 70%. Some are even approaching closer to 80%. The CRS is grade 1 and 2, it's not grade 3 or 4. There is no funky neurotoxicity we currently see with any of the bispecifics, and that is a major advantage.

It actually pains me to point out the safety profile for CAR T cells, because I love the response rates. High-grade CRS, high-grade neurotoxicity, grade 3 or higher being seen with these BCMA-directed CAR T-cell therapies. We need to address this issue and identify the patients we can move away from CAR T cells toward the bispecifics. When our community colleagues look at this safety data and they look at the bispecifics, I think they will prefer using bispecific antibodies over the CAR T-cell therapies. Especially because we keep sending their patients back because we don't have slots.

I think the landscape is going to change once the bispecifics make it to market. The other advantage with bispecifics is you can combine them with other therapies and get a higher bang for the buck. I'm just showing the teclistamab-daratumumab combination data. Even in daratumumab- or anti-CD38 antibody-refractory patients, you're seeing very high ORRs. We need these data to mature, but you're getting the same kind of PFS with teclistamab as you do with ide-cel. Why wait for CAR T-cell therapies over the bispecifics?

Bispecifics are now moving into the frontline setting. There are trials in the newly diagnosed transplant-eligible/post-transplant maintenance setting. There are trials in the transplant-ineligible setting that are being planned with teclistamab, specifically because it's the most advanced in terms of its clinical development in myeloma. Many other bispecifics are coming on its heels, looking into early lines of treatment as well. If we start seeing these bispecifics come to the fore, I think it will be very challenging to propose CAR T-cell therapy as the go-to treatment for patients.

Then we have targets beyond BCMA. GPRC5D-directed bispecific antibodies are showing very good responses even in patients who've had prior BCMA exposure. They, too, can be combined with other therapies like daratumumab and show good activity in patients who have had progression on anti-CD38 monoclonal antibodies.

If I were to summarize my arguments here, there are a lot of bispecific platforms in clinical trials. Each of them is showing very good clinical activity. The major advantage we have with bispecifics is the off-the-shelf nature. If I'm seeing a patient in clinic today, the earliest I can get them a BCMA-directed CAR-T—one that's commercially available or on a clinical trial—is about six or seven weeks from now. That's under ideal circumstances. Whereas with a bispecific antibody, I can potentially have that patient treated this week. Why wait when you can get a good bang for your buck in terms of the responses and activity? You have therapies that are subcutaneously administered. Patients, after that initial CRS monitoring period, can go on with their lives without any quality-of-life issues or commitments to being vetted into the transplant cellular therapy program for about three months for follow-up.

> **"I would make the case that, with the level of data we are seeing in clinical trials right now, bispecifics will likely replace CAR T cells and AHSCT in the newly diagnosed setting for the majority of patients."**
>
> *—Saad Z. Usmani, MD, MBA, FACP*

The potential disadvantage is the continuous therapy model. The case that I mentioned tells you that you can discontinue bispecifics. There are clinical trials right now that are asking that question. If you get a sustained response, can you discontinue treatment with the bispecifics? That one-and-done approach, it's not just something that we can say for CAR T-cell therapies. I think we'd be able to say it for bispecifics as well.

Then, moving into earlier lines of treatment, bispecifics can be combined with other mechanisms of action. That will be very hard to do with cellular therapies. So, for various reasons, I think bispecifics are going to play a big role in taking care of patients with myeloma and will beat not just CAR T-cell therapy, but may have the potential to beat autologous hematopoietic stem cell transplant (AHSCT) in the frontline setting.

The cost perspective and the access perspective are where the bispecifics can really make an impact. I think the cost of this therapy can potentially decrease, and it can be globally accessible because of the number of bispecific platforms that are in development.

I would make the case that, with the level of data we are seeing in clinical trials right now, bispecifics will likely replace CAR T cells and AHSCT in the newly diagnosed setting for the majority of patients.

Protein Expression Signatures May Be Prognostic in Pediatric AML

Take-aways:

- Recurrent protein expression patterns in pediatric AML are independently prognostic of patient outcomes.
- Certain protein expression patterns are associated with better responses to given therapies.
- Combining proteomic data with genetic risk-stratification data may help tailor and individualize therapy for patients with pediatric AML.

Protein expression patterns in patients with pediatric acute myeloid leukemia (AML) can independently predict survival outcomes and responses to certain treatments, according to a recent study.

Fieke W. Hoff, MD, PhD, of the University Medical Center Groningen at the University of Groningen in the Netherlands and the University of Texas Southwestern Medical Center, and colleagues conducted the study and published its findings in *Haematologica*.

Dr. Hoff and colleagues studied the "proteomic landscape" of pediatric AML to identify potential therapeutic targets because "with the exception of acute promyelocytic leukemia, leukemia with *FLT3*-internal tandem duplication mutations, and mixed phenotype acute leukemia, pediatric AML has been treated as a homogeneous disease, as therapy does not differ based on the underlying mutations."

The researchers previously conducted a pilot study that assessed 194 proteins in 95 patients with de novo pediatric AML, identifying eight prognostic protein expression signatures.

Dr. Hoff and colleagues used the same approach in the current study to prospectively assess samples from patients treated in a Children's Oncology Group randomized, phase III trial that evaluated the impact of adding the proteasome inhibitor bortezomib to cytarabine, daunorubicin, and etoposide.

The current study aimed to "validate the ability to classify pediatric AML patients based on proteomics in a larger cohort, with significantly more protein targets," according to the investigators. They also wanted to determine if protein classification can enhance risk stratification; identify patients who could benefit from bortezomib, cytarabine, daunorubicin, and etoposide; and identify additional potential therapeutic targets.

Study Design

The researchers collected peripheral blood samples from 500 patients with de novo pediatric AML, as well as 30 control CD34-positive bone marrow samples from 20 children and 10 adults between July 2011 and February 2017. They collected samples from all patients prior to chemotherapy.

The researchers were able to obtain samples from 92.6% of patients 10 hours after the start of induction chemotherapy and from 93.2% of patients 24 hours after the start of chemotherapy. Patients received one dose of each chemotherapeutic agent by the time samples were collected 10 hours and 24 hours after therapy.

The researchers used 296 "strictly validated" antibodies on reverse phase protein arrays to measure protein expression and activation levels in samples from patients with pediatric AML and control samples. They used the multistep MetaGalaxy analysis methodology to identify protein expression signatures "based on strong recurrent protein expression patterns," according to Dr. Hoff and colleagues.

Proteomic Profiles

The study's investigators analyzed 296 proteins and allocated them into 31 protein functional groups, with three to five protein clusters identified in each group for a total of 116 protein clusters. The researchers applied principal component analysis to graphically compare patient protein cluster expression patterns with patterns in non-malignant CD34-positive cells.

The overall proteomic profiles of patients with pediatric AML were "distinct from those of normal CD34-positive cells," but "overlapping 'normal-like' expression patterns" occurred in 27% of the protein clusters, the study's authors wrote. Protein clusters that did not have dominant co-localization on CD34-positive samples were defined as leukemia-specific clusters.

They determined seven (23%) of the protein functional groups were significantly associated with patient outcomes. One example is the heat shock protein functional group, which was divided into four protein clusters: protein cluster one, protein cluster two, protein cluster three, and protein cluster four. The heat shock protein clusters were significantly prognostic in all patients for overall survival (OS; $P=.004$), as well as for event-free survival (EFS; $P=.0009$) and relapse risk ($P=.0016$).

The heat shock protein expression cluster patterns were also prognostic for OS, EFS, and relapse risk in patients receiving bortezomib plus cytarabine, daunorubicin, and etoposide, or cytarabine, daunorubicin, and etoposide. Patients with protein cluster two who received the quadruplet had a significantly higher five-year OS rate (81%) than those who received the triplet (54%; $P=.00087$). However, patients with protein cluster four who received the triplet had a five-year OS rate of 100% (see **TABLE 1**), while those who received the quadruplet had a five-year OS rate of 67% ($P=.019$). Bortezomib did not affect patients with protein cluster one, "which was an unfavorable prognostic indicator" after treatment with the triplet or quadruplet, the authors wrote.

TABLE 1. Survival Rate by Treatment and Protein Cluster

Treatment regimen	Five-year OS of protein cluster two	Five-year OS of protein cluster four
Bortezomib plus cytarabine, daunorubicin, and etoposide	81%	67%
Cytarabine, daunorubicin, and etoposide	54%	100%

The researchers also used the 116 protein clusters identified to derive correlated protein clusters, defined as protein constellations. They then defined nine protein expression signatures "as clusters of patients who expressed similar combinations of [protein constellations]," according to Dr. Hoff and colleagues. They found 24 proteins were universally altered across all protein expression signatures, with seven proteins having universally higher expression and 17 having universally lower expression.

The protein expression signatures were associated with cytogenetics, mutation status, and patient prognosis. See **TABLE 2** for a summary of the data on protein expression signatures and prognosis. In a multivariate Cox regression analysis, unfavorable protein expression signatures remained an independent prognostic factor for OS, EFS, and relapse risk.

Dr. Hoff and colleagues also identified protein expression signatures that were associated with patient responses to therapy. In patients receiving the triplet, protein expression signatures five through eight were associated with the poorest

TABLE 2. Protein Expression Signature and Associated Prognosis

Protein expression signature	Associated prognosis
Protein signature one	Intermediate
Protein signature two	Unfavorable
Protein signature three	Favorable
Protein signature four	Intermediate
Protein signature five	Unfavorable
Protein signature six	Intermediate
Protein signature seven	Unfavorable
Protein signature eight	Intermediate
Protein signature nine	Intermediate

prognosis. Adding bortezomib to the triplet treatment improved five-year OS rates in patients with protein expression signatures six, seven, and eight.

Protein expression signature risk groups did not correlate with the risk group stratification used in the clinical trial or conventional risk group stratification. However, protein expression signatures stratified EFS and relapse risk in patients classified in the trial as low risk, defined by inv(16)/t(16;16), t(8;21), *NPM1*, or *CEBPA* mutations. Protein expression signatures one, three, six, and nine were associated with favorable prognosis, while signatures five and seven were associated with unfavorable prognosis in the low-risk patients.

Protein expression signature risk groups were also prognostic for patients who were classified as high risk in the trial, and signatures one, three, and six were associated with a favorable prognosis. However, protein expression signature nine, which was associated with a favorable prognosis in low-risk patients, was associated with a "highly unfavorable" prognosis in high-risk patients, the researchers wrote.

Proteomics 'Can Direct Therapy' in Pediatric AML

The research, which was the "largest proteomic study in pediatric AML" to the authors' knowledge, indicated the "genetic heterogeneity of pediatric AML coalesces into a finite number of recurrent protein expression patterns," Dr. Hoff and colleagues wrote.

It showed protein expression signatures can be significantly prognostic, especially combined with genetic data, "demonstrating that adding proteomics to genetic risk-stratification can direct therapy leading to improved outcome," according to the researchers.

The prognostic proteomic data may help clinicians and researchers tailor the selection and development of therapies for pediatric AML.

"In summary, we confirmed the existence of recurrent protein patterns in pediatric AML, which enabled separation of AML patients into recurrent [protein expression signatures] that were prognostic, particularly when combined with known pediatric AML risk factors," Dr. Hoff and colleagues concluded. "We identified [protein expression signatures] that benefited from [bortezomib, cytarabine, daunorubicin, and etoposide] and postulate that recognition of abnormal proteins can aid in risk stratification and therapy selection in pediatric, and perhaps adult, AML."

The study was funded in part by Takeda Pharmaceuticals.

Reference

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TP53 Mutations Linked with Lenalidomide in Therapy-Related Myeloid Neoplasms

Take-aways:

- Exposure to thalidomide analogs, particularly lenalidomide, is significantly associated with *TP53* mutations in patients with therapy-related myeloid neoplasms.
- Treatment with lenalidomide, but not pomalidomide, provides a selective advantage to preleukemic *Trp53*-mutated HSPCs.
- These data suggest a "biological rationale" for pomalidomide use in patients who are at a high risk for therapy-related myeloid neoplasms.

A new study showed a significant association between previous lenalidomide treatment and *TP53* mutations in patients with therapy-related myeloid neoplasms.

Adam S. Sperling, MD, PhD, of the Dana-Farber Cancer Institute and Brigham and Women's Hospital, and colleagues conducted the study and published the results in *Blood*.

Dr. Sperling and colleagues conducted the research because therapy-related myeloid neoplasms, which "arise from selective pressure introduced" by chemotherapy and radiation therapy "represent one of the most devastating consequences of cancer therapy," as they are frequently resistant to treatment, with a median OS of seven to 14 months.

It is crucial to understand "how individual therapies promote the outgrowth of specific mutant clones" and develop strategies to reduce the risk of therapy-related myeloid neoplasms by modifying therapies, according to the study's authors.

Consequently, Dr. Sperling and colleagues conducted a systematic analysis of the association between therapy-related myeloid neoplasm genotypes and prior chemotherapy and radiation therapy.

Methodology

The researchers retrospectively reviewed data from 416 patients with therapy-related myeloid neoplasms who were diagnosed per the 2016 World Health Organization classification and treated at a single institution between November 2008 and February 2019.

Of the 416 patients, 40% had therapy-related AML, while 60% had therapy-related myelodysplastic syndromes (MDS). Most patients (63%) had a primary diagnosis of solid tumors, while 37% had non-myeloid hematologic cancers.

Nearly half (45%) of patients received prior treatment with chemotherapy alone, while 17% received radiotherapy alone, and 39% received chemotherapy and radiotherapy. Most patients (83%) did not undergo autologous hematopoietic stem cell transplantation.

The median latency from initial chemotherapy or radiation therapy exposure to diagnosis was 6.2 years. The latency period was significantly shorter in patients who developed therapy-related AML (median latency, five years) than in those who developed therapy-related MDS (median latency, 6.4 years; $P=.0283$). See **TABLE 3**.

TABLE 3. Median Times From Initial Chemotherapy or Radiation Therapy Exposure to Therapy-Related Myeloid Neoplasm Development

Patient cohort	Median latency
All patients	6.2 years
Therapy-related MDS	6.4 years
Therapy-related AML	5.0 years

The study's authors used next-generation sequencing to perform mutation analyses on cryopreserved diagnostic bone marrow or peripheral blood samples. They also analyzed a comparison group of 1,021 patients with de novo myeloid neoplasms, including 611 patients with non-treatment-related AML and 410 with de novo MDS who were diagnosed and treated during the same time at the same institution.

Dr. Sperling and colleagues detected somatic mutations in bone marrow or peripheral blood samples from 156 of the 416 patients with therapy-related myeloid neoplasms by using hybrid capture sequencing of coding regions in 300 genes. They used the same technique in the remaining 260 patients to detect somatic mutations in 81 genes.

The researchers also conducted a multiplexed in vivo CRISPR knockout screen in hematopoietic stem and progenitor cells (HSPCs) from mice, generated Hoxb8 cell lines and Hoxb8 cell line experiments, and performed competitive bone marrow transplantation and thalidomide analog treatment in mouse models.

Frequency of Mutations

Nearly half of patients (41%) had a complex karyotype, which was −7/del(7q) in 34%, −5/del(5q) in 32%, and 11q23 rearrangements in 7%. Almost all (85%) patients with therapy-related myeloid neoplasms had at least one detectable mutation, which were primarily in *TP53* (37%) and *PPM1D* (19%). See **TABLE 4**. Multi-hit alterations occurred in 61% of *TP53*-mutated cases in combination with del(17p) or multiple *TP53* mutations. Mutations in *TET2* occurred in 16% of patients, *DNMT3A* in 15%, *RUNX1* in 13%, *ASXL1* in 13%, and *SRSF2* in 10%.

In the Literature

TABLE 4. Mutation Status of Patients with Therapy-Related Myeloid Neoplasms

Mutation status	Frequency
Patients with at least one detectable mutation	85%
Patients with no detectable mutations	15%

The researchers compared mutational frequency between patients with therapy-related AML or MDS and those with non-therapy-related AML or MDS. Mutations in *TP53* and *PPM1D* were significantly more frequent in patients with therapy-related AML or MDS, while mutations in *STAG2* and *ASXL1* were more common in patients with AML or MDS who did not previously undergo chemotherapy or radiotherapy.

Furthermore, *NPM1*, *IDH1/2*, *FLT3*, *CEBPA*, and *NRAS* mutations were enriched in patients who had AML without exposure to chemotherapy or radiotherapy. Mutations in *TET2*, *PHF6*, *SRSF2*, *SF3B1*, and *U2AF1* were more common in patients who had MDS and no prior exposure to chemotherapy or radiotherapy.

Dr. Sperling and colleagues assessed the association between mutations and prior exposure to chemotherapy and/or radiotherapy, finding a significant correlation between complex karyotype and treatment with platinum agents (odds ratio [OR], 1.88; 95% CI, 1.23-2.89). They also found a significant correlation between chromosome 7 abnormalities and alkylating agent treatment (OR, 1.64; 95% CI, 1.08-2.49) or platinum drugs (OR, 1.65; 95% CI, 1.06-2.57).

The researchers also found significant associations between *TP53* mutations and proteasome inhibitors (OR, 3.06; 95% CI, 1.52-6.15) and between *TP53* mutations and thalidomide analogs (OR, 2.62; 95% CI, 1.36-5.05).

A multivariate logistic regression analysis confirmed the significant association between *TP53* mutations and prior exposure to thalidomide analogs (OR, 3.14; 95% CI, 1.60-6.18; *P*=.0009). It also confirmed the significant association between *TP53* mutations and exposure to vinca alkaloids (OR, 1.76; 95% CI, 1.05-2.93; *P*=.031) and a significant negative association between *TP53* mutations and exposure to topoisomerase inhibitors (OR, 0.49; 95% CI, 0.26-0.91; *P*=.023).

The researchers investigated the effect of lenalidomide on mutant HSPCs because 92% of the thalidomide analog exposure in the patients studied involved lenalidomide. Lenalidomide provided a "selective advantage" to murine *Trp53*-mutant HSPCs, as lenalidomide, but not pomalidomide, led to outgrowth of *Trp53*-mutant cells in all blood cell lineages, according to Dr. Sperling and colleagues.

"The primary difference between the activities of lenalidomide and pomalidomide is the degradation of CK1α," they wrote.

Treatment Implications

The significant association between *TP53*-mutated therapy-related AML or MDS and prior exposure to thalidomide analogs, particularly lenalidomide, is likely to have treatment and prognostic implications.

For example, the study showed pomalidomide may limit "the selective advantage of *TP53*-mutant clones," which provides a "biological rationale" to use it in patients who have a high risk of developing therapy-related myeloid neoplasms, the study's authors wrote.

"These findings highlight the role of lenalidomide treatment in promoting *TP53*-mutated [therapy-related myeloid neoplasms] and offer a potential alternative strategy to mitigate the risk of [therapy-related myeloid neoplasm] development," Dr. Sperling and colleagues concluded.

Reference

Sperling AS, Guerra VA, Kennedy JA, et al. Lenalidomide promotes the development of TP53-mutated therapy-related myeloid neoplasms. *Blood*. 2022;140(16):1753-1763. doi:10.1182/blood.2021014956

Regulatory Actions

Recent therapy approvals, updates, and clinical trial results in the field of hematologic oncology

FDA Grants Priority Review to Bispecific Antibody Glofitamab for Relapsed or Refractory LBCL

The U.S. Food and Drug Administration (FDA) has granted priority review for glofitamab, an investigational CD20×CD3 T-cell-engaging bispecific antibody, for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy.

If approved, glofitamab would be the first fixed-duration, off-the-shelf CD20×CD3 T-cell-engaging bispecific antibody available to treat patients with aggressive lymphoma who have previously received multiple courses of treatment.

The Biologics License Application (BLA) submitted on behalf of glofitamab is based on positive data from the pivotal phase I/II NP30179 multicenter, open-label, dose-escalation and expansion study, which included patients who had previously received multiple courses of therapy, with 85.1% of patients refractory to their most recent therapy and approximately one-third (33.1%) having received prior chimeric antigen receptor T-cell therapy.

Results showed that 40% of patients (n=62/155) achieved a complete response (CR), and 51.6% (n=80/155) achieved an objective response (combination of CR and partial response). The median follow-up time was 13.4 months. Among those who achieved a CR, 73.1% continued to experience a response at 12 months, while the median duration of CR was not reached. The median duration of response was 18.4 months.

The most common adverse event was cytokine release syndrome (CRS), which was generally low grade (48.1% of patients had grade 1 and 12.3% had grade 2). Most CRS events were associated with initial administration of glofitamab (in cycle 1). The incidence of grade 3 or higher CRS was 3.9%, with no grade 5 events. Only one patient (n=1/155) discontinued glofitamab due to CRS.

The FDA will review the glofitamab BLA under the granted Fast Track Designation. Data from the phase I/II NP30179 study of glofitamab were submitted for review to the European Medicines Agency.

Source: Genentech, January 2023

FDA Approves Zanubrutinib for CLL, SLL in Adult Patients

The FDA has approved zanubrutinib for the treatment of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

The approval is based on two global phase III trials: the ALPINE study and SEQUOIA study. Both trials demonstrated superior efficacy for zanubrutinib in first-line and relapsed/refractory treatment settings for adult patients with CLL and SLL.

"We have seen striking data from the [zanubrutinib] development program demonstrating significant and consistent efficacy across CLL patient subtypes, including the high-risk del17p/*TP53*-mutated population, and regardless of treatment setting," **Jennifer R. Brown, MD, PhD,** Director of the CLL Center of the Division of Hematologic Malignancies at Dana-Farber Cancer Institute, said in a release from BeiGene, the manufacturer of the drug. "With extensive follow-up across the CLL development program and the combined results from the SEQUOIA and ALPINE trials, [zanubrutinib] is established as a new standard of care for CLL."

With a median follow-up of 26.2 months in the SEQUOIA trial, zanubrutinib demonstrated a significant progression-free survival benefit versus bendamustine plus rituximab (hazard ratio, 0.42; 95% CI, 0.28-0.63; $P<.0001$).

In the ALPINE trial, zanubrutinib achieved a superior overall response rate versus ibrutinib in the relapsed/refractory treatment setting (80.4% vs 72.9%; $P=.0264$).

Source: BeiGene, January 2023

FDA Receives BLA for Talquetamab in Relapsed/Refractory Multiple Myeloma

The FDA received a BLA for the use of talquetamab in patients with relapsed or refractory multiple myeloma (MM).

Talquetamab is an investigational, off-the-shelf, bispecific T-cell engager antibody targeting GPRC5D and CD3. It previously received Breakthrough Therapy Designation from the FDA in June 2022 for the treatment of adults with relapsed or refractory MM who underwent at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody.

"Despite the therapies that have been developed for the treatment of MM, there remain persistent unmet needs for patients who relapse or become refractory," said **Peter Lebowitz, MD, PhD,** Global Therapeutic Area Head of Oncology at Janssen Research and Development, in a statement. "Through our discovery and development of talquetamab … we remain relentlessly committed to the investigation of innovative therapies for patients and oncologists."

The BLA is supported by data from the phase I/II, first-in-human MonumenTAL-1 study of talquetamab in patients with relapsed or refractory MM who received more than three prior lines of therapy, Janssen officials said in a news release.

Ajai Chari, MD, of the Mount Sinai School of Medicine, and colleagues presented the phase II results of the MonumenTAL-1 study during the 2022 American Society of Hematology Annual Meeting and Exposition.

Talquetamab remains under evaluation in the phase I/II MonumenTAL-1 trial, as well as in the combination studies RedirecTT-1, TRIMM-2, TRIMM-3, MonumenTAL-2, and MonumenTAL-3.

The bispecific T-cell engager antibody received Orphan Drug Designation for MM from the FDA in May 2021. Talquetamab also received Orphan Drug Designation from the European Commission in August 2021 after receiving a PRIME designation from the commission in January 2021.

Source: Janssen, December 2022

Moxetumomab Pasudotox for Hairy Cell Leukemia to Be Withdrawn From United States Market

Moxetumomab pasudotox, a treatment for relapsed or refractory hairy cell leukemia, is expected to permanently leave the United States market this summer, according to information from the FDA and AstraZeneca, the manufacturer of the drug.

Physicians were advised in a letter that moxetumomab pasudotox would be permanently discontinued in the United States market in July 2023. It will ask its distributors to halt all distribution in August 2023, as well as request returns of the drug from distributors starting in August 2023.

The drug was approved by the FDA in September 2018 for patients with relapsed or refractory hairy cell leukemia who had at least two prior systemic therapies, including a purine nucleoside analog. It was not recommended for patients who had severe renal impairment.

The removal of the drug from the United States market is "not related to the safety or efficacy" of the product, AstraZeneca officials said in a communication to health care providers. There has been a "very low clinical uptake" of the product since its FDA approval "due to the availability of other treatment options and possibly due to the specialized complexity of administration, toxicity prophylaxis, and safety monitoring needs for patients," according to AstraZeneca.

Physicians should not initiate new treatment with the drug, with immediate effect, AstraZeneca officials said in the letter. The supply of the product to physicians will not be available after August 2023, but physicians who are currently treating patients with the drug will have "adequate time" to complete six treatment cycles.

Source: AstraZeneca, November 2022

Post-AHSCT Brentuximab Vedotin Plus Nivolumab 'Highly Active' in Hodgkin Lymphoma

Post-autologous hematopoietic stem cell transplantation (AHSCT) consolidation with brentuximab vedotin plus nivolumab was "highly active" in patients with high-risk relapsed/refractory classic Hodgkin lymphoma, according to results from a phase II trial.

Alex Herrera, MD, of the City of Hope Medical Center, and colleagues conducted the research and published their findings in *The Lancet Haematology*.

Dr. Herrera and colleagues conducted the study because post-AHSCT consolidation with brentuximab vedotin improved progression-free survival (PFS) over placebo in patients with high-risk relapsed or refractory classic Hodgkin lymphoma.

The researchers conducted the phase II trial at five centers in the United States and included 59 adults with high-risk relapsed or refractory classic Hodgkin lymphoma. Most patients (58%) were male. The patients received brentuximab vedotin 1.8 mg/kg and nivolumab 3 mg/kg intravenously on day one of up to eight 21-day cycles. Patients received the therapy 30 to 60 days after they underwent AHSCT. The median time from AHSCT to treatment was 54 days, and patients received a median of eight cycles. The median follow-up was 29.9 months.

No dose reduction was allowed for nivolumab, but a 1.2 mg/kg dose reduction was permitted for brentuximab vedotin. Patients were allowed to continue one drug if the other was discontinued due to a toxic effect. The study's primary endpoint was the 18-month PFS in all treated patients.

Nearly half (49%) of the patients completed eight cycles of brentuximab vedotin plus nivolumab, with 76% of patients completing eight cycles of at least one of the drugs. The 18-month PFS rate was 94% in all patients. Sensory peripheral neuropathy, reported in 53% of patients, was the most common adverse event, followed by neutropenia in 42%, and immune-related adverse events requiring corticosteroids in 29%. The researchers did not report any treatment-related deaths.

"Brentuximab vedotin plus nivolumab was highly active post-AHSCT consolidation for patients with high-risk relapsed or refractory classic Hodgkin lymphoma, most of whom had previous exposure to either brentuximab vedotin or PD-1 blockade," Dr. Herrera and colleagues concluded. "Combination immunotherapy in this setting should be further studied in patients with classic Hodgkin lymphoma with further refinement of the regimen to mitigate toxic effects, particularly in high-risk patients in whom more intensive therapy to prevent relapse is warranted."

Reference

Herrera AF, Chen L, Nieto Y, et al. Brentuximab vedotin plus nivolumab after autologous haematopoietic stem-cell transplantation for adult patients with high-risk classic Hodgkin lymphoma: a multicentre, phase 2 trial. *Lancet Haematol.* 2023;10(1):e14-e23. doi:10.1016/S2352-3026(22)00318-0

Better Outcomes with Active Therapy in MDS

Patients with myelodysplastic syndromes (MDS) who received active therapy soon after their diagnosis had better outcomes than those who did not, according to a recent study.

Maria Julia Montoro, MD, PhD, of the Hospital Universitari Vall d´Hebron in Barcelona, Spain, and colleagues conducted the prospective, observational ERASME study to assess the "evolution of newly diagnosed and treatment-naïve high-risk MDS patients."

The study included 204 patients who had a median age of 73 years. Nearly all (94.6%) patients had comorbidities, 69.6% had an Eastern Cooperative Oncology Group performance status score of 0-1, and 54.4% were male.

Most patients (52%) received active treatment, which was the most common strategy, followed by HSCT (25.5%) and supportive care/watchful waiting (22.5%).

The overall event-free survival (EFS) was 7.9 months. The median EFS was 9.1 months in patients receiving active treatment, 8.3 months in those who received HSCT, and 5.3 months in those undergoing supportive care/watchful waiting.

The overall PFS was 10.1 months. The median PFS was 12.9 months in patients receiving active treatment, 12.8 months in those who received HSCT, and 4.3 months in those undergoing supportive care/watchful waiting. The overall survival (OS) for all patients was 13.8 months. The median OS was 15.4 months in those receiving active treatment, 14.9 months in those who received HSCT, and 8.4 months in those undergoing supportive care/watchful waiting.

Most patients (72.6%) experienced a grade ≥3 adverse event, with 60.6% experiencing serious adverse events, and 33.1% dying due to adverse events. Second primary malignant neoplasms occurred in three patients at a median of 8.2 months.

"This study highlights the importance of initiating active treatment in newly diagnosed intermediate-2/high-risk MDS patients. This treatment group showed results with higher EFS, PFS, and OS values than those related to patients under another therapeutic strategy within the same risk group," Dr. Montoro and colleagues concluded. "Ultimately, selecting an active treatment for [high-risk] MDS patients had a protective effect against the risk of events, disease progression, and death."

Reference

Montoro MJ, Pomares H, Coll R, et al. Evaluation of the outcomes of newly diagnosed patients with high-risk myelodysplastic syndrome according to the initial therapeutical strategies chosen in usual clinical practice. *Leuk Lymphoma.* 2022. doi:10.1080/10428194.2022.2154604

This article discusses the current state of the art in the role of maintenance therapy in acute myeloid leukemia. The following material is reproduced from "SOHO State of the Art Updates and Next Questions: The Role of Maintenance Therapy in Acute Myeloid Leukemia," published in the January 2023 issue of Clinical Lymphoma, Myeloma & Leukemia. *The article was written by Rodrick Babakhanlou, MD, MSc, and Farhad Ravandi-Kashani, MD.*

The Role of Maintenance Therapy in Acute Myeloid Leukemia

Past studies investigating the role of maintenance therapy in acute myeloid leukemia (AML) were unable to demonstrate an advantage in overall survival (OS). Consequently, maintenance therapy has not been an established practice in the treatment of AML.

The most effective post-remission therapy for AML continues to be allogeneic hematopoietic stem cell transplant (HSCT). However, allogeneic HSCT is not available to all patients with high-risk disease due to the lack of suitable donors or the potential toxicity and mortality associated with the procedure. Therefore, there is a significant need for strategies like effective maintenance in patients unable to undergo allogeneic HSCT, with the goal of improving OS. This review provides a summary of prior and ongoing approaches to maintenance therapy for AML.

Maintenance Chemotherapy

Different maintenance therapy strategies for AML have been investigated for more than 40 years, including single agents and a combination of drugs or immune-based strategies. The earliest approaches to maintenance therapy of low-dose cytosine arabinoside, thioguanine, and anthracyclines were studied in randomized trials. Although some subgroups of patients experienced prolongation of remission duration and relapse-free survival, none of those trials were able to show a benefit in OS. Given the lack of OS benefit, maintenance therapy using chemotherapy is not recommended currently.

Maintenance Immunotherapy

Immunotherapy, which includes therapeutic vaccines, cytokine therapy, lenalidomide, and immune checkpoint inhibitors, has probably been the most widely studied strategy to maintenance therapy in patients with AML.

With regard to therapeutic vaccines, there have been four randomized, controlled trials (RCTs) evaluating the effects of the bacillus Calmette-Guérin (BCG) vaccine as maintenance therapy in patients with AML. Of those studies, only one, which used a combination of BCG and irradiated allogeneic AML cells, showed an improvement in remission duration and OS. The remaining three RCTs found no outcome differences between maintenance and observation.

Similarly, RCTs on cytokine therapy as a maintenance strategy for AML have found no difference in five-year disease-free survival (DFS) or OS. As a result of the negative outcomes in literature and the unpleasant side effects associated with the administration of cytokines, these methods were abandoned.

Lenalidomide, although well tolerated, also failed to show an improvement in DFS and OS and is not considered to be effective in eradicating measurable residual disease (MRD).

Immune checkpoint inhibitors targeting programmed cell death-1 and cytotoxic T-lymphocyte antigen-4 have been used for the treatment of both solid tumors and certain hematologic malignancies, such as Hodgkin lymphoma. As monotherapy, they have demonstrated limited efficacy in patients with AML. The REMAIN trial is an ongoing study evaluating the efficacy of nivolumab maintenance versus observation in adults with AML in remission after chemotherapy.

Hypomethylating Agents

Hypomethylating agents (HMA), including decitabine and azacitidine, have epigenetic activities. Both are now approved for the treatment of myelodysplastic syndromes in the United States but are also used as single agents for older patients with AML. So far, HMA maintenance does not seem to improve outcomes in younger patients with AML but does appear to be promising in older patients with AML who are not eligible for allogeneic HSCT. Based on the QUAZAR AML-001 trial, which showed an OS benefit for the oral formulation of azacitidine, it has been approved by the U.S. Food and Drug Administration (FDA) for continued therapy in patients with AML in remission.

Small-Molecule Targeted Therapies

Small-molecule targeted agents have been the focus of several studies and include *FLT3* inhibitors and the BCL-2 inhibitor venetoclax.

FLT3 inhibitors used as maintenance therapy in patients with *FLT3*-mutated AML include midostaurin, sorafenib, and gilteritinib. Based on the phase III RATIFY trial, midostaurin was approved by the European Medicines Agency; however, it has not been approved by the FDA. In the SORAML trial, patients who received sorafenib had an improved event-free survival (EFS) of 21 months versus 9.5 months in the placebo arm. There was no improvement in OS. Gilteritinib was shown to improve outcomes in relapsed and refractory *FLT3*-mutated AML, and an ongoing, phase III, randomized trial is comparing DFS in patients with *FLT3*-mutated AML who were randomized to receive either gilteritinib or placebo for an 11-year period after completion of induction/consolidation chemotherapy.

Venetoclax has shown improved outcomes in combination with HMA for older patients with newly diagnosed AML and is currently being tested in a phase II trial in which patients are treated with azacitidine and venetoclax until MRD negativity is achieved, followed by venetoclax maintenance.

Androgens

In a multicenter, prospective, randomized, open-label, phase III study, 330 patients were enrolled and randomized to norethandrolone versus placebo. Of those, 165 patients received norethandrolone. The results showed an improved DFS, EFS, and OS at one year compared with the placebo arm. In this study, the beneficial effects of norethandrolone became evident after one year and were apparent in those who had not relapsed within one year after achieving complete response (CR).

Post-Transplant Maintenance

Although allogeneic HSCT following induction and consolidation therapy in AML is highly effective in reducing the risk of relapse, unfortunately, up to 40% of patients will relapse post-HSCT and face a dismal prognosis. Maintenance therapy is intended to prolong remission and facilitate a graft-versus-leukemia effect to eradicate residual leukemia cells.

Post-transplant maintenance therapy with decitabine in combination with recombinant granulocyte colony-stimulating factor (G-CSF) was studied in an open-label, multicenter, phase II trial that included 204 patients with AML who were MRD-negative following allogeneic HSCT. The two-year cumulative relapse rate was reduced in the treatment arm compared with placebo (38.3% vs 15.0%), and the OS was superior with G-CSF and decitabine compared with placebo (85.8% vs 69.7%).

Various *FLT3* inhibitors, including sorafenib, midostaurin, and quizartinib have also been investigated in the post-transplant setting as maintenance options. Several studies reported potential benefits with those inhibitors in the setting of post-allogeneic HSCT maintenance therapy.

Need for Effective Post-Remission Strategies

Despite decades of investigation, optimal maintenance strategies for the management of AML are lacking, and there are insufficient data to support routine maintenance therapy. While the introduction of targeted therapies applied in combination with chemotherapy has improved the CR rate, the rate of relapse has remained unchanged, a fact that points to the most common cause of treatment failure in the post-consolidation setting. It is critical to consider that maintenance therapy is associated with increasing costs, exposure to long-term drug toxicity, and impaired quality of life. Moreover, there is the risk of overtreating a subset of patients who might have been cured with induction and consolidation therapy, which underlines the importance of defining the patient population that will benefit from receiving maintenance therapy. There is an urgent need to identify effective post-remission strategies, with the aim of improving DFS and OS.

Clinical Trial Updates

Blood Cancers Today *shares clinical trials currently enrolling patients*

Outcomes After CAR-T Therapy and Radiation Therapy for Hematologic Malignancies

This observational, prospective study is evaluating outcomes after chimeric antigen receptor (CAR) T-cell therapy and radiation therapy for hematologic malignancies.

"Collecting information from patients before, during, and after receiving [CAR-T] therapy or radiation therapy may help doctors to optimize patient selection, dose, timing, and sequencing of these treatments," according to the study's investigators.

The primary objective of the study is to record clinical outcomes of patients with hematologic malignancies who receive standard-of-care CAR T-cell treatment and radiation therapy.

The study's secondary objectives include:

- Recording patient-specific and treatment-related factors in this group of patients
- Recording and exploring the relationship between the radiation dose, target, technique, and timing regarding CAR T-cell therapy and clinical outcomes in patients receiving CAR T-cell therapy and radiation
- Recording and studying the relationship between patient-specific and treatment-related factors and treatment toxicity in this group of patients

The study is recruiting 100 patients. Patients must be aged 18 years or older. They must undergo treatment with or intend to receive treatment with radiation therapy and standard-of-care CAR T-cell therapy within a 90-day window for a hematologic malignancy.

Principal investigator: **Penny Q. Fang, MD**
Treatment agent: Observation
NCT04888338

Safety, Tolerability, and Pharmacokinetics of Navitoclax Monotherapy and in Combination with Ruxolitinib in MPN

This five-part study's primary objectives are to evaluate safety, tolerability, and pharmacokinetics of navitoclax when administered alone in part one or when administered in combination with ruxolitinib in part two. In part two of the study, participants must have been receiving a stable dose of ruxolitinib therapy for at least 12 weeks prior to study enrollment. In part three of the study, all eligible participants will receive navitoclax, with the primary objective being to evaluate potential navitoclax effect on QTc prolongation. In part four, the researchers will evaluate the effect of navitoclax on the pharmacokinetics, safety, and tolerability of a single dose of celecoxib. In part five, all eligible participants will receive ruxolitinib twice daily and navitoclax once daily for drug-drug interaction assessment, followed by continued administration of navitoclax in combination with ruxolitinib.

The study's primary outcome measures include:

- The number of participants with dose-limiting toxicities during the first 28-day cycle of navitoclax during parts one and two
- The maximum observed plasma concentration (C_{max}) of navitoclax in parts two and five
- The C_{max} of celecoxib in part four
- Time to the C_{max} of navitoclax in parts two and five
- Time to the C_{max} of celecoxib in part four
- The area under the plasma concentration-time curve from time zero to the time of the last measurable concentration of navitoclax
- The area under the plasma concentration-time curve from time zero to the last measurable concentration of celecoxib
- The number of participants with adverse events from first dose of study drug until 30 days following last dose of study drug, up to approximately five years
- Change in QT interval corrected for heart rate interval by Fridericia's correction formula during part three

The study's secondary outcome measure is the overall response rate over 96 weeks, according to the International Working Group (IWG)-Myeloproliferative Neoplasms Research and Treatment/European LeukemiaNet criteria for participants with myelofibrosis, essential thrombocythemia, and polycythemia vera, and according to IWG criteria for participants with chronic myelomonocytic leukemia.

Study director: **AbbVie**
Treatment agents: Navitoclax, ruxolitinib, and celecoxib
NCT04041050

BAFFR-Targeting CAR T Cells for the Treatment of Relapsed or Refractory B-Cell ALL

This phase I trial is evaluating the side effects and best dose of B-cell activating factor receptor (BAFFR) CAR T cells in patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). BAFFR-specific CAR T cells may help the body's immune system identify and kill BAFFR-positive cancer cells.

The primary outcome measure is the incidence of adverse events up to one year after treatment, with toxicities followed from the start of lymphodepletion until the end of the study. Secondary outcome measures include disease response, minimal residual disease, B-cell frequency, severity of graft-versus-host disease in patients who previously received allogeneic hematopoietic stem cell transplantation, progression-free survival, and overall survival.

Principal investigator: **Ibrahim Aldoss, MD**
Treatment agent: BAFFR-CAR T cells
NCT04690595

Assessing Anti-CD38 Antibody-Drug Conjugate in Relapsed or Refractory Multiple Myeloma

This clinical trial is a two-stage, phase Ib/IIa, open-label, multicenter, dose-escalation study of STI-6129. Patients with relapsed or refractory multiple myeloma will receive the anti-CD38 antibody-drug conjugate intravenously once in a four-week cycle.

The study aims to identify the recommended phase II dose of STI-6129 by assessing the safety, preliminary efficacy, and pharmacokinetics using a 3+3 study design for dose escalation in stage one. The second stage will be an expansion study to assess preliminary efficacy.

The investigators will enroll patients sequentially within each cohort and between cohorts during the dose escalation portion of the study, with a 28-day cycle of treatment.

The primary outcome measure is the safety of STI-6129. Secondary outcome measures include the pharmacokinetic profile of STI-6129, the overall response and duration, and preliminary efficacy.

Investigators: **Rajshekar Chakraborty, MD,** and **David Kaminetzky, MD**
Treatment agent: STI-6129
NCT05308225

HemOnc Happenings

Reporting on recent announcements, awards, and appointments in the hematology/oncology sphere

ASPHO Announces Awards, Lectureships

The American Society of Pediatric Hematology/Oncology (ASPHO) recently named the recipients of its 2023 Distinguished Career Award, Frank A. Oski Memorial Lectureship, and George R. Buchanan Lectureship Award.

A. Kim Ritchey, MD

A. Kim Ritchey, MD, of the Children's Hospital of Pittsburgh, received the ASPHO Distinguished Career Award.

The award is presented annually to "a senior physician or other professional who during his or her career has had a major impact on the subspecialty through some combination of research, education, patient care, and advocacy," according to ASPHO.

Dr. Ritchey, a pediatric hematologic oncologist, is a Professor of Pediatrics and Vice Chair of International Affairs in the Department of Pediatrics at the Children's Hospital of Pittsburgh. He has "extensive experience caring for children with blood diseases and cancer, participates and leads clinical investigation in the field, and has mentored numerous trainees in the clinical and clinical research settings. He is the departmental representative for all aspects of international activity," according to his biography from the Children's Hospital of Pittsburgh.

Saro Armenian, DO, MPH

ASPHO awarded the 2023 Frank A. Oski Memorial Lectureship to **Saro Armenian, DO, MPH,** of the City of Hope.

ASPHO awards the lectureship annually to an "outstanding clinical or laboratory investigator in pediatric hematology/oncology whose cutting-edge research is of the caliber of the investigations made by Dr. Oski," according to ASPHO.

The lectureship's purpose is to "honor Dr. Oski's many contributions to the field of pediatric hematology/oncology and ensure a younger generation of pediatric hematology/oncology specialists remains aware of his legacy," ASPHO officials said.

Dr. Armenian is the Barron Hilton Chair and Professor of Pediatrics and the Director of the Division of Outcomes Research within the Department of Population Sciences at the City of Hope. He is a co-leader of the Comprehensive Cancer Center Cancer Control and Population Sciences Program and directs the Center for Survivorship and Outcomes in the Hematologic Malignancies Research Institute.

"Since joining City of Hope in 2008, Dr. Armenian has been enormously successful in achieving international recognition as a physician-scientist focused on improving the health outcomes of childhood and adult-onset cancer patients," according to his biography from the City of Hope.

Michael Pulsipher, MD

Michael Pulsipher, MD, of the University of Utah Health, received the ASPHO 2023 George R. Buchanan Lectureship Award.

The award annually recognizes a "national/international expert in pediatric hematology/oncology" and serves to "honor Dr. Buchanan and assure that future generations of pediatric hematology/oncology specialists are aware of his significant contributions to ASPHO and the field."

Dr. Pulsipher is Chief of the Division of Pediatric Hematology/Oncology at the Intermountain Primary Children's Hospital, Director of the Children's and Adolescent Cancer Initiative at the Huntsman Cancer Institute, and a Presidential Chair in Pediatric Oncology and Hematology at the University of Utah.

"Dr. Pulsipher's work in cell therapy helped lead to the [U.S. Food and Drug Administration] approval of the first [chimeric antigen receptor (CAR) T-cell] treatment, tisagenlecleucel, and he continues to run trials in CAR T-cell], [natural killer], and viral specific T-cell therapies," according to his biography from the University of Utah Health.

Source: ASPHO, December 2022

ASH Elects New Members to Executive Committee

The American Society of Hematology (ASH) recently announced the election of four new members to its Executive Committee for terms that began after the 2022 ASH Annual Meeting and Exposition in December.

Belinda R. Avalos, MD

Belinda R. Avalos, MD, will serve a one-year term as vice president followed by successive terms as president-elect and president. **Joseph Mikhael, MD, MEd,** will serve a four-year term as treasurer. **Christopher R. Flowers, MD, MSc,** and **Charlotte M. Niemeyer, MD, MA,** will each serve four-year terms as councilors.

Joseph Mikhael, MD, MEd

"Drs. Avalos, Mikhael, Flowers, and Niemeyer have demonstrated immense dedication to ASH, its members, and the field of hematology," current ASH President, **Jane N. Winter, MD,** of the Robert H. Lurie Comprehensive Cancer Center at Northwestern University, said in a statement. "Under their leadership, the society will be well-positioned to lead our field in education, cutting-edge research, and advocacy on behalf of patients with blood disorders worldwide."

Christopher R. Flowers, MD, MSc

As a "distinguished physician-scientist, [Dr. Avalos] has made significant research contributions in the areas of leukemogenesis, congenital neutropenia, transplantation, and cellular therapy," ASH officials said in a press release.

Dr. Avalos, a Professor of Medicine and a Senior Advisor to the President of Atrium Health Levine Cancer Institute, "has also championed minority recruitment and retention in hematology," the press release said.

Charlotte M. Niemeyer, MD, MA

Dr. Mikhael is a Professor in the Applied Cancer Research and Drug Discovery Division at the Translational Genomics Research Institute (TGen). He is also the Chair of the Diversity, Equity, and Inclusion Council at TGen and Chief Medical Officer of the International Myeloma Foundation.

"Dr. Mikhael's research focuses include multiple myeloma, health disparities, education, and health communications," ASH officials said in a news release. "A member of ASH for more than 20 years, he has served ASH on numerous committees and editorial boards, currently serving as associate editor of *ASH Clinical News*."

Dr. Flowers, Professor and Chair of the Department of Lymphoma and Myeloma at the University of Texas MD Anderson Cancer Center, currently serves as the Chair of the Committee on Diversity, Equity, and Inclusion and is "an active and supportive mentor" in the ASH Minority Medical Student Award Program, according to ASH officials. He was honored with the 2022 ASH Mentor Award.

"His research interests include clinical lymphoma; evidence-based clinical practice guidelines development; and epidemiological, translational, and outcomes research studies," ASH officials said.

Dr. Niemeyer is a Professor of Pediatrics and Director of the Division of Pediatric Hematology and Oncology in the Department of Pediatrics at Freiburg University Medical Center.

"She previously served as Chair and Vice Chair of the International Members Committee [and] the Scientific Committee on Blood Disorders in Childhood [and] Vice Chair of the *Blood* Editor Search Committee, among other prominent roles in ASH committees," ASH officials said.

Her research interests include diagnosis and therapy for bone marrow failure disorders, pediatric myelodysplastic syndromes, and juvenile myelomonocytic leukemia, according to the news release.

Source: ASH news release, October 2022

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HISTORY OF THE SOCIETY OF HEMATOLOGIC ONCOLOGY

Over the course of the last decade, it has been recognized by hematologists and hematologist oncologists that the amount of research and interest in the field of hematologic oncology has increased to the point that the exchange of information could not be accomplished at the other major scientific societies. It was clear that this specialized group needed an opportunity to focus on these malignancies, and to have a meeting where outstanding leaders, innovators and budding young investigators, could interact to stimulate progress in this important field. In 2012, the decision was made to form a new society, the **Society of Hematologic Oncology** (SOHO), which would sponsor an annual meeting to bring together leading investigators and practitioners in the field.

Today, SOHO is a non-profit association committed to promoting worldwide research, education, prevention, clinical studies and optimal patient care in all aspects of hematologic malignancies and related disorders.

GLOBAL REACH

SOHO represents physicians and other health care professionals from all corners of the world. The SOHO global network supports and is supported by nearly 6,000 members from 122 countries, who are leading vital efforts to further treatments for patients with hematologic malignancies. The society is an organization that focuses on learning and educational excellence, and promotes diversity and inclusion.